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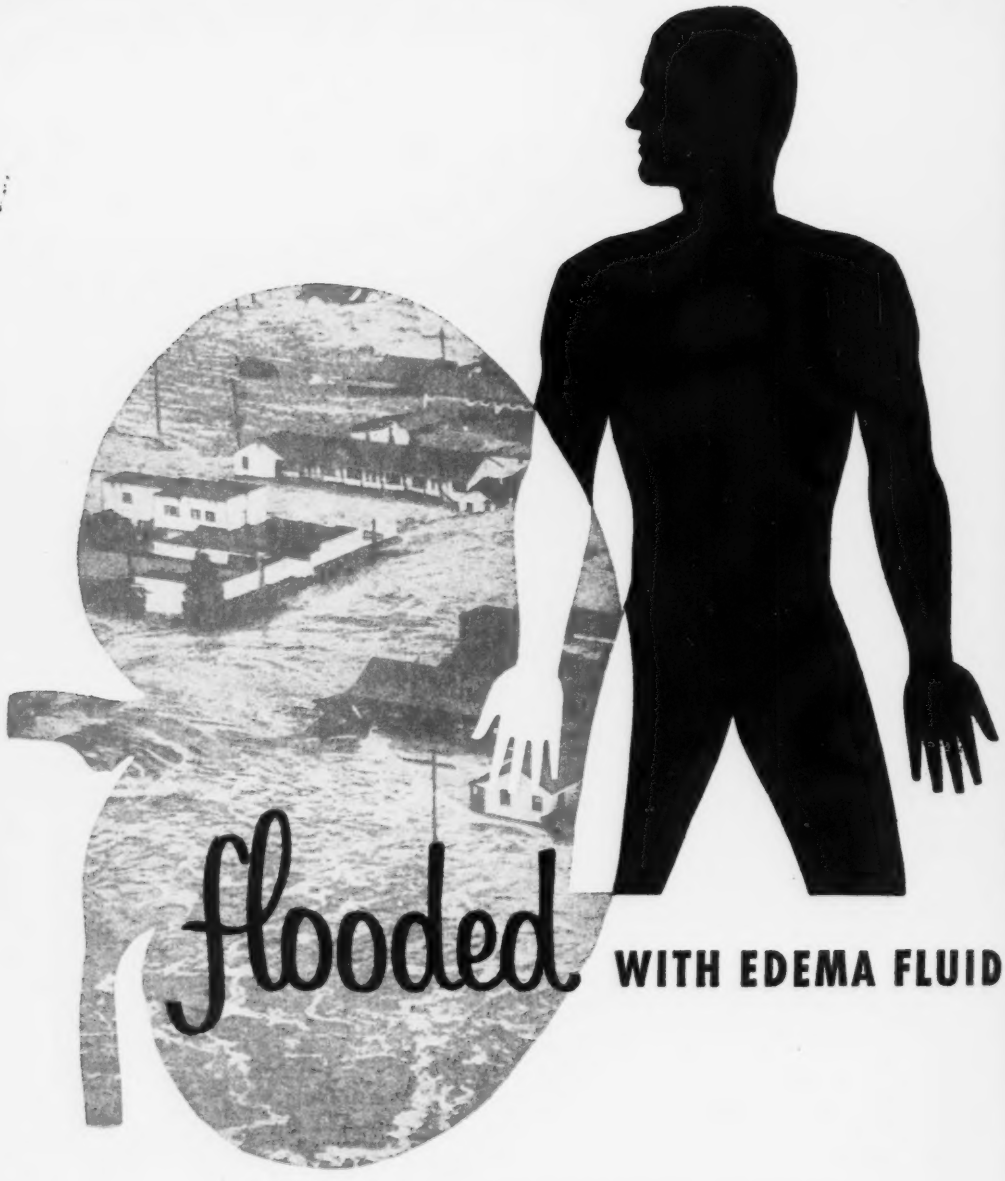

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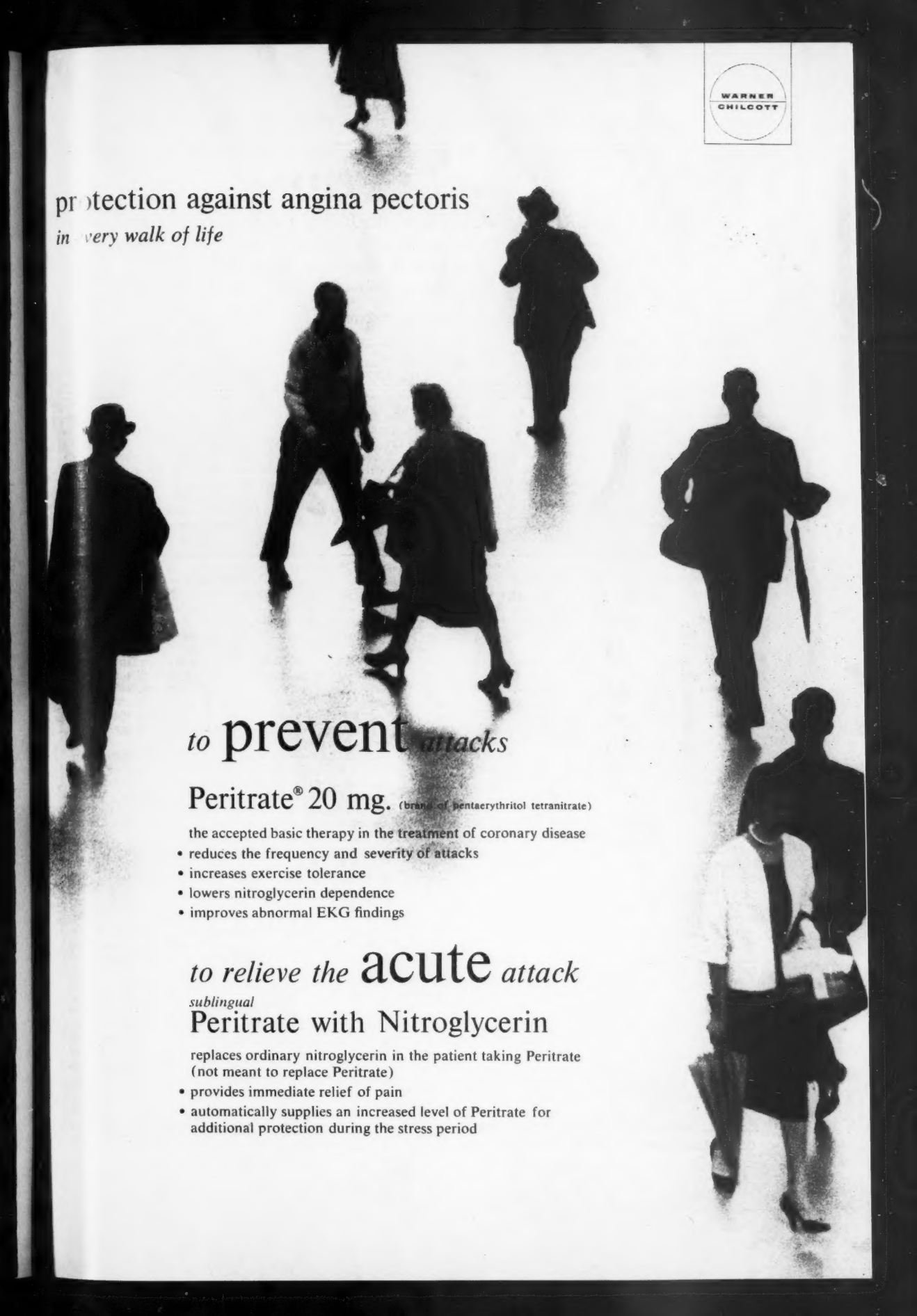
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Editorial

Explanation in Cardiologic Practice

ADVANCES in knowledge of disorders of the heart and circulatory system during the past 50 years have resulted in more accurate diagnosis, improved treatment, more reliable estimates of prognosis, and a hopeful attitude toward the possible fruits of further clinical and laboratory research. It has become evident that the ultimate goal of preventing all forms of heart disease is far from an idle dream. But with all this progress, surprisingly little attention has been paid to one fundamentally important feature of cardiologic practice. Neither in undergraduate teaching nor in internship and residency training programs is sufficient emphasis given to the need for explaining to the patient the nature of his problem, the mechanism and significance of his symptoms, and the course the illness may be expected to follow. This is unfortunate, for in most if not all forms of heart disease and in functional disturbances suggesting cardiac pathology an explanation along these lines is essential if the best possible response to treatment is to be obtained. As matters stand at present, it may be several years after graduation before a young physician fully appreciates all that can be accomplished by sufficiently detailed instruction of those under his care.

There are many cardiac problems in which the difference between a satisfactory and a poor therapeutic result is determined largely by the care with which the patient carries out the recommended program of treatment. Attention to details may gain years of comfortable and productive life, and whether or not a person cooperates to the extent required usually depends on whether or not he understands the need for the measures advised. Angina pectoris due to coronary atherosclerosis supplies an excellent example. There is no statistical evidence that the prognosis of this condition is affected significantly by drug therapy. Treatment, therefore, is directed principally toward protecting the patient from habits, activities and emotional situations that increase the hazards of the syndrome. It is essential that the person have a clear understanding of the problem. The pathogenesis of the symptoms and the mode of action of the various factors that may induce attacks must be discussed in detail, and reasons should be given for weight reduction in overweight persons, avoidance of overeating, resting after meals, abstaining from tobacco and observing extra precautions during cold weather. Emphasis is placed on the importance of avoiding the seizures, but at the same time reasonable assurance is given as to the patient's relative safety so long as he remains free from pain. Mention also should be made of the possibility that with time an effective collateral circulation may develop and bring with it an appreciable improvement in exercise capacity, but in order to avoid misunderstanding it must be pointed out that there is no way of telling beforehand which patients will fall in this fortunate group. The therapeutic and prophylactic use of nitroglycerin should be explained, and possible objections to the use of the drug should be forestalled by a brief description of the potential side effects, with

stress on their harmlessness, and by assurance that repeated use of the preparation is not injurious in any way. A reminder should be given at the same time that even though the drug is not harmful a person is not thereby excused from exercising all possible care to avoid attacks. A talk along these lines places the problem in its true light and often greatly reduces the patient's anxiety and apprehension. This in turn may result in a considerable diminution in the frequency of the seizures.

Acute myocardial infarction rarely occurs at a time convenient for the patient. After the pain and other symptoms have been controlled, the physician often finds that he is dealing with a person who is not only frightened and bewildered but also depressed and resentful. One of the most helpful things one can do at this time is to take a few minutes to explain as clearly as possible what it is that has happened and what is entailed in the healing of an infarct. Frequently it is advisable to mention that within a few days the patient may begin to feel better than he has for some time but that this will not lessen the need for thorough treatment. Estimates should then be given as to the probable length of hospitalization and as to when the person may expect to be allowed up in a chair, go to the bathroom, begin increasing his daily activities and return to work. At his next visit after this discussion, the physician often finds a remarkably changed patient and one who obviously has made the first great readjustment to his illness.

Initial attacks of congestive heart failure usually respond promptly to treatment, but success in long-term management can be expected only if the patient is well informed concerning his problem. Regardless of the type of underlying heart disease, there must be careful instruction in the general concept of myocardial reserve, the significance of dyspnea and other symptoms, and the importance of each of the measures included in the treatment schedule. One of the commonest reasons for recurrences of cardiac decompensation is failure on the part of the patient to observe the necessary degree of sodium restriction in the diet. A simple discussion of the role of sodium in water retention will usually insure against lapses of this kind. Certain persons object to taking digitalis because they erroneously regard it as a heart stimulant employed only late in the course of cardiac disease, and there are others who, contrary to directions, will discontinue its use after having been restored to a state of comfort. These errors can be prevented by a brief description of the effects of the drug on the efficiency of the myocardium and, in atrial fibrillation, on the ventricular rate.

Means have become available within recent years for reducing the incidence of certain forms of heart disease, but these measures are not as yet being used to full advantage. Most initial and recurrent attacks of rheumatic fever can be prevented by early and adequate treatment of streptococcal sore throat, and patients who have rheumatic heart disease or who have had rheumatic fever or chorea can be protected from streptococcal infections and possible further cardiac damage by the year-round use of sulfadiazine or penicillin. Many cases of bacterial endocarditis can be averted by administering appropriate antimicrobial drugs to patients with rheumatic valvular disease or congenital cardiac anomalies before dental extractions, removal of tonsils and adenoids, obstetrical delivery, and operations on the urinary or lower gastrointestinal tract. The maximum benefit from these advances in preventive cardiology will not be realized, however, until convincing information about them reaches everyone concerned in any way with problems of these kinds. Parents, teachers and physicians must be thoroughly instructed in the symptoms and signs of streptococcal sore throat and in the need for prompt, specific treatment. Patients who have rheumatic valvular disease or congenital cardiac anomalies (or, in the case of infants and children, their parents) should be made aware of the presence of the abnormality and of the indications for prophylactic antibiotic therapy. In all instances, the instruction must be given in such a manner that the person has no difficulty in appreciating the importance of the measures advised.

Anxiety, insecurity, emotional tension and fatigue often are responsible for symptoms that cause the patient concern about his heart. The commonest and most troublesome of these symptoms is sticking or aching pain in the precordial area. The exact mechanism of the discomfort is not known but that it is not due to heart disease is well established. The pain is not retrosternal in location and does not radiate to that region. At times, however, it spreads upward toward the left shoulder and even down the left arm but usually along the lateral, not the medial, aspect. The sharp or sticking variety may be of no more than momentary duration, but the dull or aching type and that which is described as a sense of heaviness frequently lasts for hours at a time. The distress is not induced by physical activity but may develop after a period of exertion. Rest and nitroglycerin fail to give prompt relief. A careful history and physical examination followed by assurance that the pain is arising in the chest wall and is the result of overwork or nervous strain often results in prompt improvement or even complete relief. It is essential that there be a positive explanation of the discomfort. A statement that there is no heart disease without further elaboration leaves many questions unanswered in the patient's mind and seldom convinces him of the harmlessness of his symptoms.

Premature beats frequently cause anxiety because of disagreeable sensations resulting from the ectopic contractions themselves, the following compensatory pause or the extra force of the next normal beat. In other instances the arrhythmia causes no symptoms, and its presence is discovered accidentally by persons who make it a practice to feel their radial pulse. A diagrammatic explanation of the disturbance and reassurance as to its harmlessness often are the only therapeutic measures necessary. The common relationship to fatigue, emotional tension, and excessive use of coffee or tobacco should be discussed, and it often is especially helpful to point out that premature beats occur while the patient is at rest and usually can be abolished by physical activity. It also is advisable to mention that ectopic contractions will not strain or damage a normal heart regardless of the length of time they persist or the frequency with which they occur.

The nonmedical public is well informed of the fact that shortness of breath is a common symptom of organic heart disease, and this often is responsible for erroneous self diagnosis. Many tense and apprehensive persons come to their physicians quite certain that the respiratory difficulty they have been experiencing is due to some serious cardiac disorder. Observation reveals occasional or frequent sighing, and there may be periodic, deep, forced inspiration, at times of such degree that the accessory muscles of respiration are brought into action. The patient complains of a sense of suffocation and a feeling that during inspiration air will not pass beyond a certain point in the midchest. Sighing respiration and these other features are parts of the hyperventilation syndrome, which with rare exceptions is a psychosomatic disorder. The overbreathing results in a reduction in the carbon dioxide content of the arterial blood, and this in turn may cause fatigue, weakness, dizziness or lightheadedness, heart consciousness, numbness or coldness of the hands and feet, soreness or aching in the muscles of the thorax, back, or extremities, and in unusual instances tetany with carpopedal spasm. It is chiefly the respiratory distress and heart consciousness that arouse fear of cardiac disease. The other symptoms are often interpreted by the patient as manifestations of an impending cerebral vascular accident. Reassurance that the dyspnea is due to emotional tension and not organic disease, and an explanation of the relation between the other symptoms and reduced arterial carbon dioxide content, usually lessen the patient's concern and bring about clinical improvement. The beneficial effects of these measures can be reinforced by demonstrating on the patient that voluntary hyperventilation reproduces the symptoms and that breath-holding or rebreathing from a paper bag then gives prompt relief.

One of the most frequently repeated criticisms of the physician of today is a seeming lack of sympathetic interest in his patients.

The public is aware of the advantages of scientific diagnosis and treatment, but it takes these more and more for granted and desires in addition personal attention comparable to that given by the family doctor of the past. There is a desire in each of us to be recognized as an individual, and because of this no one enjoys being looked upon solely as an example of a particular disease or syndrome. Furthermore, people come to their doctors because of concern about their symptoms, and even though the self assurance of the physician may convince them of the correctness of his diagnosis, their anxiety is seldom allayed unless time is taken after the diagnostic studies to explain the illness, the reasons for the therapeutic measures advised, and the general prognosis. The discussion should include as much practical information as may be of use to the patient, and inquiries should be encouraged and answered patiently. Certain persons fail to ask questions because of timidity, fear of appearing ignorant, or apprehension about the answers. With experience, an observant clinician acquires increasing insight into human nature and becomes intuitively aware of much that the patient under his care would like to know. These points should be covered in a more or less incidental manner in the course of the final summary. Instruction of this kind, given unhurriedly and in understandable terms, convincingly indicates true interest and effectively replaces much that was included in the personal service of the old-school family doctor. To omit it because of thoughtlessness or the pressure of one's practice constitutes neglect of a basic obligation to the patient and failure to employ a therapeutic tool of indispensable importance. There is need for more attention to this facet of cardiologic practice in undergraduate teaching and in internship and residency training programs.

A. CARLTON ERNSTENE

The physician needs a clear head and a kind heart; his work is arduous and complex, requiring the exercise of the very highest faculties of the mind, while constantly appealing to the emotions and finer feelings.—WILLIAM OSLER. *Teaching and Thinking.* Montreal Med. Journal, 1895.

Relationship of Amount of Cigarette Smoking to Coronary Heart Disease Mortality Rates in Men

By Robert W. Buechley, M.A., Robert M. Drake, M.D., M.P.H., and Lester Breslow, M.D., M.P.H.

Seven out of 8 previous reports indicate a relationship between morbidity or mortality from coronary heart disease and amount of cigarette smoking. Data from 2 California study groups, longshoremen and respondents to a household sample health survey, are presented to show similar relationships. In 4 studies showing mortality, the coronary heart disease death rates for men, in various age groups from 40 to 70 years, who smoked a pack of cigarettes or more per day, generally exceeded the corresponding rates for nonsmokers by from 1 to 7 deaths per thousand per year.

BERKSON, among others, has pointed out that lung cancer is not the only cause of death, for which increased mortality is observed among heavy cigarette smokers.[1] While mortality from lung cancer is many times higher among heavy smokers than it is among nonsmokers, this increased risk pertains to a still relatively infrequent cause of death. The proportional excess of mortality associated with cigarette smoking is less in the case of coronary heart disease, but this increased risk pertains to the most common cause of death, especially of males in the middle years. The Hammond and Horn data indicate 4 times as many excess deaths, associated with cigarette smoking,[2] from coronary heart disease as from lung cancer.

The purpose of this paper is to present, for comparison, the several studies that provide mortality rates by smoking class for coronary heart disease; and the several case-control studies that show coronary cases and controls by smoking class, including 1 study of each type, based on California data.

We consider that these findings, especially their consistency, raise the question whether cigarette smoking may carry greater risk for coronary heart disease than for lung cancer.

In the following pages the reported studies are summarized. As far as the varied reporting systems allow, these have been reduced to comparability. Comparisons may thus be made, and implications drawn, by each reader for himself.

Previous Reports

The positive relationship of smoking to coronary heart disease in men was first reported for Mayo Clinic patients by English, Willius and Berkson in 1940,[3] following Pearl's 1938 report of an increase in total mortality with amount of cigarette smoking.[4] Mills reported an excess of smokers,[5] and greater amounts of smoking[6] in cases of death from coronary heart disease. Gertler and White[7] found more smokers among cases than among controls. Hegglin and Keiser in Switzerland[8] found more and heavier smokers among male coronary cases. Hammond and Horn[2, 9] and Doll and Hill[10] reported significantly higher mortality rates from coronary heart disease in heavier smokers. The Framingham study, reporting incidence of coronary disease by smoking class, had nonconfirmatory results.[11]

The Study Group on Smoking and Health, sponsored by the American Cancer Society, the American Heart Association, the National Cancer Institute, and the National Heart Institute, recommended " . . . a research program of wide scope that would clarify the relationship and association between smoking

From the California State Department of Public Health, Berkeley, Calif.

This study was supported in part by funds from the Heart Disease Control Program, Division of Special Health Services, and in part by a grant from the National Institutes of Health, U.S. Public Health Service.

TABLE 1.—*Deaths and Mortality Rates of Coronary Heart Disease in Men per 1,000 Person-Years of Risk*

Age group	Total, all cigarette smoking classes			Smoking class by daily amount												Difference in death rate between non-smokers and smokers of about 1 pack per day or more
				Non-smokers			Light smokers			Moderate smokers			Heavy smokers			
	Person-years	Deaths	Death rate	Person-years	Deaths	Death rate	Person-years	Deaths	Death rate	Person-years	Deaths	Death rate	Person-years	Deaths	Death rate	
Hammond and Horn (1958)[2]*							Less than ½ pack			One-half to 1 pack			One pack or more			
50–54	111770	541	4.8	33255	90	2.71	9392	35	3.73	39226	213	5.43	29897	203	6.79	4.08
55–59	89422	629	7.25	32920	142	4.31	8432	50	5.93	29385	258	8.78	18685	199	10.65	6.34
60–64	59419	617	10.38	27817	204	7.33	5698	49	8.60	16762	235	14.02	9142	129	14.11	6.78
65–69	37348	562	15.04	21892	273	12.47	3664	58	15.83	8037	158	19.66	3755	73	19.44	6.97
Doll and Hill (1956)[1]*							1-14 Gm.			15-24 Gm.			25 Gm. or more			
35–54	73367	90	1.23	11266	5	.44	23102	22	.95	23751	35	1.47	15248	28	1.84	1.40
55–64	19909	122	6.13	1907	14	7.34	6333	43	6.79	6514	29	4.45	5155	36	6.98	−0.36
65–74	12462	143	11.47	1078	12	11.13	5201	56	10.77	3893	41	10.53	2290	34	14.85	3.72
75 & over	7459	153	20.51	856	13	15.19	3950	79	20.00	1931	43	22.27	722	18	24.93	9.74
Mills (1956)[6]*†							Less than 15 cigarettes			More than 15 cigarettes						
30–39	114595	29	.20	13624	2	.12	10642	5	.38				90329	22	.19	.05
40–49	43240	83	1.54	7912	6	.61	3623	3	.66				31705	74	1.87	1.26
50–59	35413	171	3.86	9095	25	2.20	4246	16	3.02				22072	130	4.71	2.51
Buechley, Drake and Breslow (1958)[14]*				Less than one pack						One pack or more						
35–44	5480	10	1.82				3100	4	1.29				2380	6	2.52	1.23
45–54	6920	19	2.75				4285	7	1.63				2635	12	4.55	2.92
55–64	4370	35	8.01				2990	19	6.35				1380	16	11.59	5.24
65–74	1389	14	10.14				1170	12	10.23				210	2	9.52	−0.74

* Smokers of only pipes and cigars are excluded in Hammond and Horn and in our recomputation of Mills. They are distributed by grams of tobacco in Doll and Hill's report, and are included in light and non-smokers in our study of longshoremen.

† Rates for all cardiovascular disease, computed from Mills' data, have been reduced by 20 per cent to approximate coronary heart disease rates.

2, 10, 6 and 14: See references.

Longshoremen: unpublished data, California Department of Public Health.

and cardiovascular disease." Of particular importance, they considered, were "epidemiologic studies with appropriate consideration of the roles of other factors such as diet, physical activity, and blood lipids."[12]

California Findings

Information on cigarette smoking and data concerning coronary heart disease are available for 2 California populations.

The first is a population of 3,994 longshoremen who received a multiphasic screening examination in 1951 and for whom 5 years of follow-up have recently been completed.[13, 14] The examined men were volunteers from a population of about 6,000 longshoremen, and selection bias occurred—the unexamined men showing higher mortality. The abbreviated question on current (1951) amount of cigarette smoking asked at this examination allows a division of the examined men into 2 classes: light or nonsmokers (less than a pack of cigarettes per day) and heavy smokers (a pack or more per day, or sometimes 2 packs). In the first 5 years of follow-up, 78 deaths from coronary heart disease* occurred among

*International Statistical Classification codes 420.0, 420.1, and 420.2.

men in the examined group. California coronary age-sex-specific death rates applied to the examined population indicate 119 expected deaths. It is thus evident that the mortality rate of coronary heart disease was lower among the examined longshoremen than in a comparable age-sex population of California, and this finding has been discussed elsewhere.[14] Of the observed deaths, 42 occurred among light or nonsmokers, compared to an expected 84, and 36 occurred among heavy smokers, compared to an expected 35. Similar proportions of observed to expected were not found for deaths from any heart disease other than coronary. Table 1 presents the basic data on coronary death rates for these men.

A retrospective case-control study, by questionnaire and interview, has been made of Californians reporting coronary disease to the California Health Survey; matched controls came from the same survey, which was based upon a representative sample of the State's population.[15] The persons selected for restudy reported their coronary heart disease, and having survived at least the first coronary attack they also are in this sense a selected group. The 116 males with coronary disease reported a much higher mean amount of smoking, averaging about 16 cigarettes per day, than the 121 controls, who averaged about 10 cigarettes per day. Twenty-three male coronary patients were nonsmokers, compared to 51 matched controls. Table 2 gives the basic data for these men. Contrary to the trend in the prospective studies of mortality, the differences in amount of smoking are larger at the older ages for this case-control study of coronary heart disease morbidity.

Mortality Study Comparisons

Substantial agreement in results is shown by the 4 prospective studies presented in table 1. These investigations, including our own study of longshoremen, generally show higher mortality rates from coronary heart disease in each successively higher smoking class. As a simple measure of over-all increase, the difference in mortality rate between the nonsmokers and the heavy smokers in each study at each age has been noted in the last column of the table. Similar differences can, of course, be computed for the rates in the other smoking classes.

The 4 reported studies cannot be exactly reduced to any common denominator, as was done by Edwards for lung cancer,[16] although the rates given in table 1 are a first step in so doing. Our study of longshoremen did not distinguish smoking categories in sufficient detail. Mill's study did not distinguish the various cardiovascular conditions. Doll and Hill lumped all types of smoking—cigar, pipe, and cigarettes—and reported on grams of tobacco smoked. Hammond and Horn avoided these difficulties, and their reporting as made in 1958 could well be taken as a model. They have adopted Doll and Hill's method of reporting person-years of exposure, which is necessary for computing commensurable rates.

Case/Control Ratios and Incidence Rate Comparisons

The studies presented in table 2, mostly case-control studies, are even more heterogeneous. The California study and the Framingham study both utilize cases identified in a representative sample of a specified population. Most of the others report on patients drawn from unknown population bases and compared with controls from the same or other bases. The Framingham study reports an incidence rate, while the other studies report numbers of cases and controls. Despite this heterogeneity, higher case-control ratios for coronary heart disease generally appear in successively higher smoking classes. Gertler and White discount the importance of this increase, although the difference they report is significant by the χ^2 test. The Framingham investigators did not consider that the data in their original report demonstrated an association with amount of smoking, but they are continuing to accumulate more data. All other investigators note the relationship, Sigler to the extent of saying "... tobacco merely may have some influence in expediting the development of coronary heart disease in a small proportion of the population ..."[17] and

TABLE 2.—*Five Studies of Case-Control Ratios of Coronary Heart Disease in Men. One Study of Incidence Rates*

Study	Age group	Numbers	Smoking class by daily amount											
			Non-smokers			Light smokers			Moderate smokers			Heavy smokers		
		Cases/controls	Cases	Controls	Case-control ratio	Cases	Controls	Case-control ratio	Cases	Controls	Case-control ratio	Cases	Controls	Case-control ratio
						About ¼ to ½ pack			About 1 pack			About 1½ to 2 packs		
California Health Survey	All ages	116/121[a]	23	51	45	27	27	100	42	29	145	21	14	1
	Under 45	5/6	0	1	0	1	1	100	0	2	0	3	2	1
	45–54	24/24	2	8	25	5	5	100	10	5	200	7	6	1
	55–64	41/43	8	15	53	8	9	89	13	13	100	10	6	1
	65–74	32/34	7	17	41	10	10	100	14	7	200	1	0	
	75 and over	14/14	6	10	60	3	2	150	5	2	250	0	0	
						Less than 1 pack			1 pack or more but less than 2			2 packs or more		
Hegglin and Keiser[8]	All under 50	153/151	10	38	26	79	81	98	49	28	175	15	4	375
									Any amount					
English, Willius and Berkson[3]	All ages	1000/1000	302	337	90				698	663	105			
	40–49	187/302	38	115	33				179	187	79			
	50–59	382/371	108	97	111				274	274	100			
	60 and over	431/327	156	125	125				275	202	136			
									Any amount					
Gertler and White[7]	All under 40	90/139	9	32	28				81	107	76			
			b (See footnote)						Any amount[c]					
Mills, 1950[5]	All ages	352/1040	85	307	28				267	733	36			
	20–29	2/351	0	88	0				2	263	1			
	30–39	8/183	0	42	0				8	141	6			
	40–49	51/196	4	43	9				47	153	31			
	50–59	120/158	9	46	20				111	112	99			
	60–69	103/90	28	40	70				75	50	150			
	70 and over	68/62	44	48	92				24	14	171			
	Age group	New cases population[d]	Incidence rate[e]	New cases	Population	Incidence rate[e]	New cases	Population	Incidence rate[e]	New cases	Population	Incidence rate[e]	New cases	Population	Incidence rate[e]
				b (See footnote)			Less than 1 pack			1 pack or more but less than 2			2 packs or more		
Framingham[11]	45/62	42/612	69	9	107	84	10	167	60	17	283	60	6	55	109

[a] Totals include 3 cases and 4 controls who smoked, but whose amount of smoking was not stated.

[b] Men who smoke pipe and/or cigar only are excluded from these recomputations

[c] Any smoking combination that includes cigarettes.

[d] Persons of unknown smoking class have been excluded.

[e] Per thousand for 4 years.

8, 3, 7, 5, and 11: See references.

California Health Survey: unpublished data, California Department of Public Health.

Hegglin and Keiser to the extent of saying that . . . smoking is now the most dangerous drug addiction."[8]

Conclusions

The heterogeneity of populations, differing approaches and manner of reporting make impossible a good estimation of the magnitude of the relationship between cigarette smoking and coronary heart disease. We have abandoned our attempts to make such an estimate from a combination of studies by various authors. However, the extent of the relationship is generally indicated by the difference in death rate between nonsmokers and heavy smokers. These differences show a strong and consistent reationship between cigarette smoking and coronary heart disease mortality, at least in men 40 to 70 years of age. The difference in mortality between cigarette smokers and nonsmokers at different ages varies from 1 to 7 excess deaths from coronary heart disease per 1,000 men per year.

Smoking rates in the United States are high,[18] and coronary death rates are also high, in comparison with many other countries.[19] Further studies of their relationship are needed.

Summario in Interlingua

Le heterogeneitate del segmentos demographic studiate e le differentias inter le principios organisatori del studios e inter le formas in que lor resultatos es reportate non permitte utilisar un combination de studios per varie autores como base de un solide estimation del grado de correlation inter le fumar de cigarettas e le incidentia de morbo cardiac coronari. Nos ha abandonate nostre effortos in iste direction. Tamen, le magnitude del correlation es reflectite de maniera general per le differentias del mortalitate ab morbo cardiac coronari inter non-fumatores e fortefumatores. Iste differentias exhibi un forte e systematic relation inter le fumar de cigarettas e le mortalitate ab morbo cardiac coronari, al minus in masculos de inter 40 e 70 annos de etate. Le differentia inter le mortalitates ab morbo cardiac coronari in fumatores de cigarettas e non-fumatores a varie etates amonta a un excesso de inter 1 e 7 mortes per anno in le fumatores.

Le incidentia del habitude de fumar in le Statos Unite es alte; le incidentia de morte ab morbo coronari es etiam alte. Le relation inter le duo require studios additional.

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SCIENCE AND PHILOSOPHY

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The philosophical outlook is synoptic; an all-round view. Science and philosophy are complementary. To the scientific thinker philosophy is of service in helping him to recognize the limitations of his task. On the other side, a modern philosophy must take account of all the far-reaching results of scientific inquiry. Thus an adequate interpretative system must have been receptive to all the influences of such conclusions as the principle of the conservation of energy, the doctrine of organic evolution, and the outstanding facts of heredity. Philosophy begins where the experimental and observational sciences leave off, but it does not follow that philosophy in its edifice must use the building-stones just as science hands them over. Thus the results of modern study of heredity need not be accepted in a form so crude that the inevitable outcome is fatalism. Similarly, when philosophy takes over from the biologist the formula of organic evolution that the present is the child of the past and the parent of the future, it is bound to scrutinize the concept of evolution and to show that it is no easy one. The general *fact* of evolution stands firmer than ever; but inquiry into the *factors* is still relatively young.—*The Outline of Science,* Vol. 4, p. 1165. From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

Congenital Aortic Stenosis

Clinical and Hemodynamic Findings, Surgical Technic, and Results of Operation

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Ten years ago congenital aortic stenosis was generally considered to be uncommon and seldom to carry a grave prognosis. The severity of obstruction of left ventricular outflow could not be directly assessed and suitable surgical procedures for its correction were not available. The changing concepts in respect to this malformation are reflected in the series of 30 patients described. The lesion was found to be relatively common and frequently serious. The severity and site of obstruction could be precisely evaluated and a physiologic basis was provided for the selection of patients for operation providing direct exposure of the aortic valve.

CONGENITAL aortic stenosis has long been considered to be an unusual and relatively benign form of congenital heart disease. However, recent reports[1-5] have called attention to the variability of the clinical course in patients presenting the classic physical findings of this lesion. With the development of technics for the surgical correction of aortic stenosis, precise evaluation of the severity of obstruction has become necessary in the proper selection of patients for operation. This has been made possible by the development of safe methods for the measurement of left heart pressure.[6, 7] The present report summarizes the clinical and hemodynamic findings in 30 patients, in all of whom the diagnosis of aortic stenosis was confirmed by the demonstration of a systolic pressure gradient between the left ventricle and a systemic artery. The technic of operative correction under direct vision and the results of surgical treatment in 18 of these patients are also presented.

CLINICAL OBSERVATIONS

The pertinent clinical and electrocardiographic findings are summarized in table 1. A history of rheumatic fever was not elicited in any of the 30 patients and none had clinical or hemodynamic evidence of involvement of the mitral valve. A heart murmur had been described in 21 patients before the age of 6 years. Nine patients, though their murmurs had been discovered later, are also included. Two of these 9 patients had other congenital cardiovascular anomalies (J. G. and W. D.). The other 7 patients had never been examined prior to the detection of their murmurs between the ages of 6 and 15 years.

There were 20 males and 10 females; their ages at admission ranged from 4 to 39 years. Three patients had associated patent ductus arteriosus (G. G., J. R., and L. A.), 1 a coarctation (J. G.), and another congenital complete heart block (W. D.). The anatomic site of obstruction was established at the time of operation or preoperative left heart catheterization in 21 patients. Valvular aortic stenosis was found in 13 patients and subvalvular stenosis in 8. In the 9 remaining patients the obstruction has not been localized and the site of stenosis is therefore designated "indeterminate" in the tables.

Of the 13 patients with valvular stenosis, 7 had angina and in 2 of these it was severe; 3 patients had experienced syncopal attacks. Twelve of these 13 patients experienced dyspnea and 4 were severely limited by this symptom. Fatigability was marked and generally associated with dyspnea. Only 1 patient (H. S.) had had right heart failure and 1

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TABLE 1.—*Clinical Features in Congenital Aortic Stenosis*

			History						Physical Exam		ECG	Operation
Site of stenosis	Patient	Age (yrs.), sex	Age murmur detected, (yrs.)	Fatigability	Dyspnea	Angina	Syncope	Duration symptoms, (yrs.)	Aortic 2nd sound	Diastolic murmur Gr. I-VI	Ventric. hypertrophy	
	R. S.	4M	½	++	++	+++	+	1	D	0	LVH	open, perfusio
	G. G.	6F	birth	+	+	0	0	2	D	0	LVH	open, hypothe a.
V	E. R.	12F	1	0	0	0	0	2	D	1	LVH	open, hypothe a.
A	D. S.	13M	1	+	+	0	0	½	D	0	LVH	open, hypothe a.
L	D. M.	16M	birth	++	++	+	0	1	D	0	LVH	none
V	C. M.	18M	birth	+	+	+	0	2	N	2	LVH	none
U	N. S.	18F	10	++	+++	0	0	1	N	2	LVH	open, hypothe a.
L	G. K.	20M	6	0	++	0	0	6	D	0	LVH	closed, transa t.
A	J. B.	26M	12	0	+	0	0	14	D	0	LVH	closed, transa t.
R	H. S.	31M	4	+++	+++	+++	+++	10	D	2	LVH	closed, transa t.
	C. W.	32M	8	+++	+++	++	0	14	N	0	LVH	open, hypothe n.
	J. T.	33M	5	+	+	+	0	1	N	0	LVH	open, hypother n.
	S. D.	39F	birth	+	+++	++	+++	3	N	0	LVH	open, perfusio
S	C. C.	8F	3	+++	+++	+++	+++	4	D	0	NH	open, perfusio
U	G. B.	10M	3	++	++	0	++	2	N	1	LVH	operat. elsewhere
B	M. S.	15F	15	0	0	0	0	—	D	0	LVH	open, hypotherm.
V	R. R.	16M	9	++	++	+++	0	9	D	2	LVH	open, hypotherm.
A	H. L.	16M	3	0	0	0	0	—	D	3	LVH	open, hypotherm.
L	C. G.	20M	12	+	++	+	0	4	N	0	LVH	none
V	A. Z.	22F	birth	++	+++	+++	0	16	N	2	LVH	open, hypotherm.
U	M. M.	36F	birth	+	++	0	0	4	N	0	LVH	open, hypotherm.
L												
A												
R												
I	C. McG.	6F	birth	0	0	0	0	—	N	0	LVH	none
N	J. R.	6F	birth	+	0	0	0	1	D	0	LVH	none
D	J. D.	8M	½	0	0	0	0	—	N	0	NH	none
E	W. F.	9M	½	++	0	0	++	4	N	0	LVH	closed, transventr.
T	D. F.	9M	birth	0	0	0	0	—	N	0	NH	none
E	W. D.	13M	13	0	0	0	0	—	N	0	CHB	none
R	M. F.	15M	1½	0	+	0	0	½	N	0	NH	none
M	L. A.	15M	birth	++	++	+	0	13	N	Cont.	LVH	none
I	J. G.	17M	17	0	0	0	0	—	N	0	NH	none
N												
A												
T												
E												

0 = Absent, + = mild, ++ = moderate, +++ = severe, D = diminished, N = normal, LVH = left ventricular hypertrophy, NH = no hypertrophy, Cont. = continuous murmur, CHB = complete heart block.

(R. S.) had experienced pulmonary edema. Only 1 patient was entirely asymptomatic.

Of the 8 patients with subvalvular stenosis, angina was severe in 3 and mild in another; 2 had histories of syncope. Six of these patients had dyspnea and 2 were severely limited by this symptom. None gave a history of right heart failure or of pulmonary edema. Two patients with subvalvular stenosis were entirely asymptomatic.

It was of interest that the only three physically underdeveloped patients of the entire group all had associated patent ductus arteriosus. Every patient had a harsh systolic mur-

TABLE 2A.—*Left Heart Catheterization Data in Patients with Valvular Congenital Aortic Stenosis*

Site of Stenosis	Patient	Status	Method	L. V. S/D (mm. Hg)	Arterial S/D (mm. Hg)	Aortic valve gradient (mm. Hg)	Orifice size† (cm.² /M.² BSA)	L. A. Mean (mm. Hg)
	R. S.	Preop.	P. C.*	270/10	110/61 FA	160	.20	—
	G. G.	Preop.	P. C.*	124/18	101/50 FA	23	—	—
	E. R.	Preop.	T. B.	221/18	117/68 FA	104	—	13
		Postop.	P. C.*	95/6	90/55 FA	5	—	—
	D. S.	Preop.	T. B.	200/10	110/65 FA	90	—	10
V	D. M.	Preop.	T. B.*	230/12	105/80 AO	125	.26	13
A	C. M.	Preop.	T. B.	160/8	130/72 BA	30	—	4
L	N. S.	Preop.	T. B.	184/8	83/54 BA	101	—	12
V		Postop.	T. B.	145/14	145/64 BA	0	—	—
U	G. K.	Preop.	T. B.	227/13	116/76 AO	111	—	12
L		Postop.	T. B.	220/21	134/82 BA	86	—	—
A	J. B.	Preop.	T. B.	230/17	120/74 BA	110	—	12
R		Postop.	T. B.	175/9	125/86 BA	50	—	9
	H. S.	Preop.	T. B.	227/15	83/42 AO	144	—	15
		Postop.	T. B.	200/12	140/68 BA	60	—	12
	C. W.	Preop.	P. C.	146/2	77/60 BA	69	—	—
		Postop.	T. B.	176/8	153/74 BA	23	.83	10
	J. T.	Preop.	T. B.	210/7	122/72 BA	88	.50	14
		Postop.	T. B.	180/18	110/65 AO	70	—	12
	S. D.	Preop.	T. B.	208/10	119/72 BA	89	.57	10

T.B. = transbronchial left heart catheterization. P. C. = percutaneous left ventricular puncture. L. V. = left ventricular pressure, FA = femoral arterial pressure. BA = brachial arterial pressure. AO = central aortic pressure.

*Procedure carried out under general anesthesia.

†Calculated effective valves are in cm.² per M.² of body surface area.

murmur and a thrill at the base of the heart, which were usually more noticeable to the right of the sternum. A high-pitched, decrescendo diastolic murmur along the left sternal border was also present in 4 of the 13 patients with valvular stenosis and in 4 of the 8 patients with subvalvular lesions. The second heart sound in the aortic area was diminished in 8 of the patients with valvular stenosis and in 3 of the group with subvalvular stenosis. Diminished peripheral arterial pulsations were not uniformly noted.

Fluoroscopic and radiographic examinations of the heart revealed some degree of left ventricular enlargement in all but 3 of the 30 patients. Characteristically this was the globular shadow of concentric hypertrophy and was most prominent in the left anterior oblique projection. Poststenotic dilatation of the aorta was a prominent feature in almost every patient. Angiocardiography was carried out in 11 patients and always revealed a thickened left ventricular wall and a small left ventricular cavity. In 1 patient (W.F.)

TABLE 2B.—*Left Heart Catheterization Data in Patients with Subvalvular Stenosis and with Indeterminate Site of Obstruction*

Site of stenosis	Patient	Status	Method	L. V. S/D (mm. Hg)	Arterial S/D (mm. Hg)	Aortic valve gradient (mm. Hg)	Orifice size (cm.² /M.² BSA)	L. A. (mm.
SUBVALVULAR	C. C.	Preop.	P. C.*	175/5	100/60 FA	75	.48	6
		Postop.	At op.*	95/5	95/50 BA	0	Cardiac output 4.44 L.	
	G. B.	Preop.	T. B.	170/9	120/80 FA	50	——	9
	M. S.	Preop.	T. B.	269/19	138/69 FA	131	——	16
		Postop.	P. C.	164/0	98/55 AO	66	——	—
	R. R.	Preop.	T. B.	294/15	122/75 AO	172	——	7
		Postop.	T. B.	115/7	120/75 FA	0	——	7
	H. L.	Preop.	T. B.	175/14	104/53 FA	61	——	—
		Postop.	At op.	110/11	103/53 AO	7	——	—
	C. G.	Preop.	T. B.	176/20	111/71 AO	65	.37	14
	A. Z.	Preop.	T. B.	230/18	110/70 AO	120	——	13
		Postop.	T. B.	200/14	140/75 FA	60	——	17
	M. M.	Preop.	T. B.	226/14	114/71 FA	112	——	6
INDETERMINATE	C. McG.	Preop.	P. C.*	125/5	90/55 FA	35	.85	—
	J. R.	Preop.	P. C.*	192/22	140/65 BA	52	1 yr. after closure	PDA
	J. D.	Preop.	P. C.*	138/5	113/67 FA	25	1.12	—
	W. F.	Preop.	At op.*	172/14	80/60 AO	92	——	—
		Postop.	At op.*	96/4	80/60 BA	16	——	—
	D. F.	Preop.	P. C.	190/11	104/59 BA	86	——	—
	W. D.	Preop.	P. C.	139/7	124/80 FA	15	——	—
	M. F.	Preop.	T. B.	154/14	114/74 AO	40	.45 after ligation PDA	13
	L. A.	Preop.	At op.*	209/28	165/74 BA	44		
	J. G.	Preop.	T. B.	173/7	118/82 BA	55	——	8

* Symbols and abbreviations as in table 2A.

the left atrium was also enlarged. In all patients without patent ductus, the chambers of the right heart were of normal size. Of the 30 patients, the electrocardiogram revealed left ventricular hypertrophy, according to criteria previously described,[8] in 24. Complete heart block with a normal supraventricular complex was present in 1 patient (W. D.).

HEMODYNAMIC FINDINGS

Left heart pressures were measured in all patients and these data are summarized in tables 2A and 2B. Left heart catheterization was performed by the transbronchial route[6, 9] in 19 patients. In the other patients, particularly young children, left ventricular pressures were obtained by means of direct puncture of this chamber through the left anterior

chest wall, as described by Brock.[7] In these patients, general anesthesia was employed and it was also required in several children catheterized by the transbronchial route. The aortic valve gradients, i.e., the differences between simultaneous peak systolic pressures in the left ventricle and the aorta or a peripheral artery, ranged from 15 to 172 mm. Hg and averaged 82 mm. Hg. Typical left ventricular and arterial pressures, recorded in the course of transbronchial left heart catheterization, are shown in figure 1. Left ventricular end-diastolic pressures ranged from 2 to 28 mm. Hg and averaged 13 mm. Hg. Cardiac outputs were measured by means of the indicator-dilution technic at the time of left heart catheterization,[9] in 10 of the patients in whom there was no evidence of aortic regurgitation. This made possible the application of the Gorlin formula[10] for the estimation of effective orifice size. These areas ranged from 0.20 to 1.12 cm.^{2} per M.^{2} of body surface area (BSA).

In 4 of the patients with subvalvular stenosis the transbronchial catheter was passed from the left ventricle into the aorta; when the catheter was withdrawn, a zone of intermediate pressure was encountered between the aorta and left ventricle that indicated the presence of the subvalvular obstruction (fig. 2). In other patients a single, abrupt pressure change was noted upon withdrawal of the catheter into the left ventricle and the presence of valvular stenosis could thus be established prior to operation.

In the patients without aortic diastolic murmurs, the direct systemic arterial pulse pressures were frequently normal but ranged from 28 to 75 mm. Hg; the average value was 4[illegible] mm. Hg. On the other hand, in the 8 patients in whom such a murmur was present, the arterial pulse pressures were often wider and ranged from 40 to 70 mm. Hg; the average value was 55 mm. Hg. In 2 such patients, presenting the clinical findings of associated aortic regurgitation, aortic regurgitant flow was estimated before operation by means of the indicator-dilution method recently described.[11] In H. L., a patient with subvalvular stenosis, the regurgitant flow was 1.4 L./min.; in patient D. S., with valvular stenosis, it was 1.6 L./min.

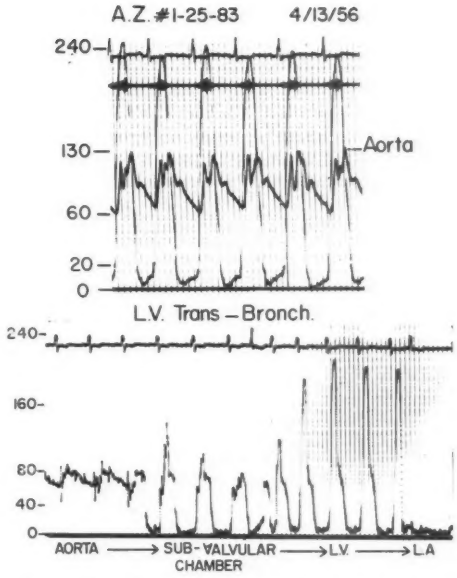


FIG. 1 *Top.* Simultaneous records of central aortic and left ventricular pressure obtained at simultaneous transbronchial left heart and retrograde aortic catheterizations. There is a peak systolic gradient of 120 mm. Hg. *(Reproduced by permission from Progress in Cardiovascular Diseases* **1**: *80, 1958)*[5]

FIG. 2 *Bottom.* Pressure tracings recorded in patient R. R. with subvalvular stenosis. Transbronchial catheter was withdrawn across aortic valve, through subvalvular chamber and then across subvalvular membrane into main left ventricular cavity (L.V.) and left atrium (L.A.). These tracings were made in the course of the same left heart catheterization summarized in table 2B but at a different time. Left ventricular pressure and gradient in table 2B are maximums observed.

Right heart catheterizations were carried out in 28 of the 30 patients. These data are summarized in tables 3A and 3B. The mean pulmonary capillary wedge pressure was measured in 25 patients in the resting state was found to be elevated above 12 mm. Hg in only 7 patients without associated patent ductus. Significant pulmonary hypertension was present in only 1 patient without an associated ductus (W. F.). In 6 other patients without patent ductus the mean pulmonary artery pressure was minimally elevated at rest (20 to 24 mm. Hg). One patient, C. G., pre-

TABLE 3A.—*Right Heart Catheterization Data in Patients with Valvular Aortic Stenosis*

Site of stenosis	Patient	Status	Condition	PC mean (mm. Hg)	PA S/D m (mm. Hg)	RV S/D (mm. Hg)	RA mean (mm. Hg)	Cardiac index (L./min./M.² BSA)	$VO_2/M.^2$
V	R. S.	Preop.	Rest	9	24/7 14	27/0	0	—	—
A	G. G.	Preop.	Rest	—	27/13 19	28/4	3	—	—
L	E. R.	Preop.	Rest	16	34/14 23	35/10	7	—	—
		Postop.	Rest	—	35/15 24	35/7	7	3.53	14
V			Exer.	18	36/22 27	—	—	6.40	38
U	D. S.	Preop.	Rest	7	27/12 18	37/5	4	—	—
L	D. M.	Preop.	Rest	12	23/15 19	30/3	3	4.29	15
			Exer.	—	42/30 36	—	—	6.56	39
A	C. M.	Preop.	Rest	8	20/4 10	20/0	1	2.79	12
R			Exer.	9	27/5 14	—	—	4.75	36
	N. S.	Preop.	Rest	14	30/15 24	35/4	3	—	—
	G. K.	Preop.	Rest	16	32/17 22	46/12	10	4.13	—
	J. B.	Preop.	Rest	17	32/16 20	37/3	4	2.58	15
		Postop.	Rest	14	24/7 17	35/9	6	5.40	15
	H. S.	Preop.	Rest	9	27/9 17	28/5	3	2.88	12
		Postop.	Rest	7	32/8 17	43/4	—	—	—
	C. W.	Preop.	Rest	8	25/8 15	30/5	3	4.61	14
			Exer.	10	35/15 20	—	—	6.19	30
		Postop.	Rest	4	19/8 14	32/2	3	2.85	14
			Exer.	1	25/13 20	—	—	5.68	45
	J. T.	Preop.	Rest	15	30/10 15	33/4	4	3.45	14
			Exer.	20	48/22 31	—	—	7.85	46
		Postop.	Rest	9	30/10 14	30/0	3	2.51	10
			Exer.	—	35/10 20	—	—	5.11	40
	S. D.	Preop.	Rest	7	18/4 8	30/2	−1	—	—

PC = mean pulmonary capillary wedge pressure. PA = pulmonary artery systolic (S), diastolic (D), and mean (m) pressures. RV = right ventricular and RA = right atrial mean pressure. $VO_2/M.^2$ = oxygen consumption per minute per square meter body surface area.

sented clear evidence of subvalvular pulmonary stenosis with a systolic pressure gradient of 16 mm. Hg across the right ventricular outflow tract. Several other patients had smaller but significant gradients (tables 3A and 3B). These observations suggest encroachment by the enlarged left ventricle on the interventricular septum and right ventricular outflow tract. In the course of right heart catheterization cardiac outputs were determined by the Fick method. In 10 patients the resting oxygen consumptions ranged from 106 to 156 ml./min./M.² BSA; these data were associated with basal respiratory quotients and indicated that the calculated cardiac outputs were representative of the steady basal state. The cardiac indices ranged from 1.50 to 4.61 and averaged 3.28 L./min./M.² BSA.

OPERATIVE TECHNIC

Eighteen patients with congenital aortic stenosis have been operated upon at the National Heart Institute. In the first 4 patients

TABLE 3B.—*Right Heart Catheterization Data in Patients with Subvalvular Stenosis and with Indeterminate Site of Obstruction**

Site of stenosis	Patient	Status	Condition	PC mean (mm. Hg)	PA S/D m (mm. Hg)	RV S/D (mm. Hg)	RA mean (mm. Hg)	Cardiac index (L./min./M.² BSA)	$VO_2/M.^2$
	C. C.	Preop.	Rest	6	27/10 16	27/0	6	—	—
S	M. S.	Preop.	Rest	11	35/7 20	33/5	2	3.60	120
I		Postop.	Rest	7	28/9 —	35/5	2	2.95	128
I			Exer.	10	33/14 18	—	—	3.66	360
V									
S	R. R.	Preop.	Rest	10	30/11 15	32/3	3	—	—
I		Postop.	Rest	8	28/9 16	30/2	3	—	—
V			Exer.	—	33/8 23	. .	—	—	—
I									
I	H. L.	Preop.	Rest	11	22/9 13	29/4	3	1.50	113
A									
I	C. G.	Preop.	Rest	12	20/12 15	71/4	3	3.00	147
	A. Z.	Preop.	Rest	15	29/12 19	27/5	2	—	—
	M. M.	Preop.	Rest	3	. — —	35/5	1	—	—
	C. McG.	Preop.	Rest	8	27/13 15	27/0	2	—	—
I	J. R.	Preop.	Rest	9	45/12 24	65/5	3	1 yr. after closure patent ductus	
N									
D									
E	J. D.	Preop.	Rest	.7	30/10 16	36/—	—	—	—
T									
E	W. F.	Preop.	Rest	22	58/34 46	58/6	4	—	—
R		Postop.	Rest	6	22/7 11	22/2	—	—	—
M									
I	D. F.	Preop.	Rest	—	25/10 15	32/4	5	—	—
N									
A	W. D.	Preop.	Rest	—	35/17 26	32/2	—	—	—
T			Exer.	—	41/22 31	—	—	—	—
E	M. F.	Preop.	Rest	10	23/8 15	25/5	4	—	—
	L. A.	Preop.	Rest	28	85/55 70	85/6	3	With patent ductus	
			Rest	7	50/20 28	42/0	2	after closure	

* Symbols and abbreviations as in table 3A.

a closed transaortic or transventricular operation was employed. Operation under direct vision by means of general hypothermia was carried out in the next 11, and the last 3 operations were performed with the aid of extracorporeal circulation and elective cardiac arrest with the patients at normal temperature. The open operation with hypothermia was employed after its safety and simplicity had been demonstrated in this laboratory by Kaiser, Gaertner, and Kay.[12] The clinical application of a similar technic has been reported by Swan[4] and Lewis.[13]

The management of patients undergoing general hypothermia in this clinic has been described.[14] Because of the experimental demonstration of myocardial failure following hypothermia and inflow occlusion, and its prevention by digitalis glycosides,[15] all patients were digitalized preoperatively. Patients were cooled by immersion to an ultimate esophageal temperature of 30 to 32 C. When

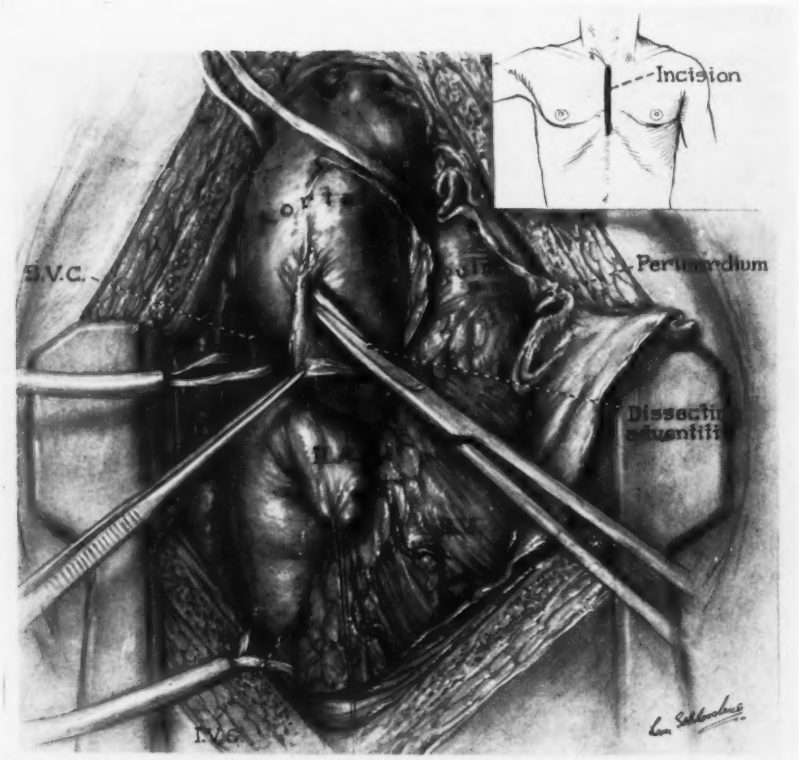


FIG. 3. Preliminary dissection following median sternotomy. The entire ascending aorta is freed from the pulmonary artery and stripped of pericardium and adventitia.

the operation under direct vision is carried out at normal temperature and with the aid of extracorporeal circulation, a Kay-Cross oxygenator with occlusive roller pumps is employed.

When either hypothermia or perfusion is used, a complete median sternotomy is made and the right pleural space and pericardium are opened wide (fig. 3). Tapes are passed about the superior and inferior venae cavae within the pericardium and the entire ascending aorta is freed of pericardium and adventitia and separated from the pulmonary artery. This dissection is carried as close as possible to the aortic annulus and is facilitated by retraction of the right atrial appendage and the fat pad in the atrioventricular groove. Care must be taken to avoid injury to the right coronary artery.

A partially occluding clamp is applied to the anterolateral wall of the aorta excluding a segment 2 to 3 cm. in length (fig. 4). An incision is made in the excluded aorta and stay sutures are placed. The venae cavae are occluded (hypothermia) or cannulated and occluded (extracorporeal circulation) and the aorta is cross clamped just below the innominate artery. With perfusion the heart is stopped by the injection of 2.5 per cent potassium citrate in blood into the occluded aorta. The aortic incision is opened, its margins are carefully retracted, and the residual blood is aspirated from the aorta and the left ventricle. The valve is easily visualized (fig. 5). If valvular stenosis is present, the commissures are carefully identified and divided in turn with scissors (fig. 6*B*). The commissures are cut to within a few millimeters of the

artic wall and their division is then completed with a Brock or Bailey dilator. If the valve is found not to be stenotic, the leaflets are grasped and retracted by an assistant. The subvalvular obstruction may then be cut, dilated, or resected with a Brock infundibular punch (fig. 6*A*).

After the obstruction has been relieved, residual air is flushed from the left ventricle and aorta, the partially occluding clamp is reapplied, the cross clamp removed, and the aortic incision closed with a continuous suture. The periods of inflow occlusion have varied from 2 to 5 minutes with hypothermia. Measurements of the valve gradient and cardiac output have ordinarily been made before and after valvulotomy. The details of these techniques have been described elsewhere.[16]

Results of Operation

Of the 18 patients operated upon, 15 are alive and free of cardiovascular symptoms. One patient (D. S.) died of irreversible ventricular fibrillation following the period of inflow occlusion. Another (H. L.) developed Pseudomonas septicemia and died 5 weeks postoperatively; at autopsy infected granulation tissue was present in the aortic suture line. The third patient (S. D.) died 10 days postoperatively from massive intrathoracic hemorrhage following the administration of heparin and Dicumarol given in the treatment of femoral thrombophlebitis. No bleeding point could be identified at autopsy; the aortic incision was well healed. One patient (G. G.) had recurrent right pleural effusions for several months and another, (J. B.) operated upon by the closed transaortic route, developed epileptiform seizures 6 months postoperatively. The relationship between the onset of these seizures and the operation is obscure. One patient (R. R.) exhibits the electrocardiographic configuration of left bundle-branch block in postoperative tracings.

Postoperatively the systolic murmur was usually decreased in intensity but was never abolished and was sometimes unchanged. In the relatively short follow-up period significant reductions in heart size have not consistently been observed. In general, postoperative electrocardiograms have shown a tendency toward normal in the amplitude of RV_6 and SV_1 (fig. 7).

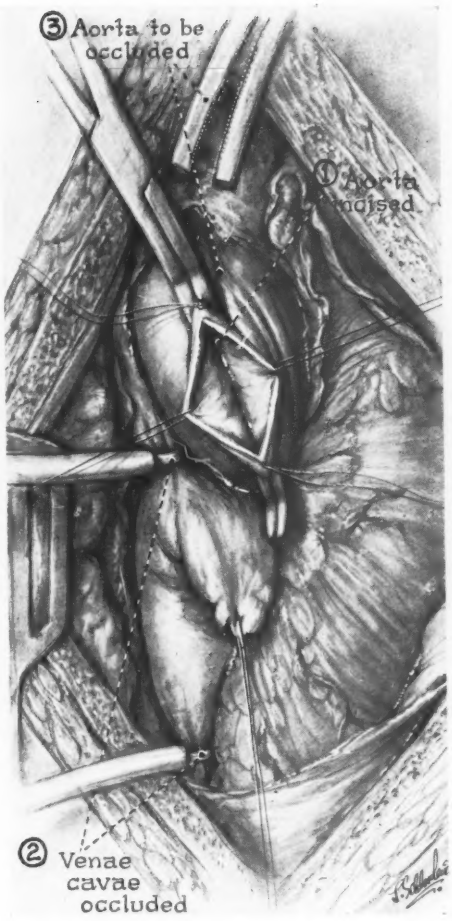


Fig. 4. Aortotomy is made within a partially occluding clamp and its edges are retracted. When extracorporeal circulation is employed, venae cavae and femoral artery are cannulated at this time.

To date, postoperative measurements of left heart pressures have been carried out in 13 of the patients operated upon. The aortic valve gradient was found to be decreased in every instance (fig. 8), but was abolished in only 3 patients. The aortic valve gradients fell from 18 to 172 mm. Hg and the average decrease was 72 mm. Hg. In the 1 patient

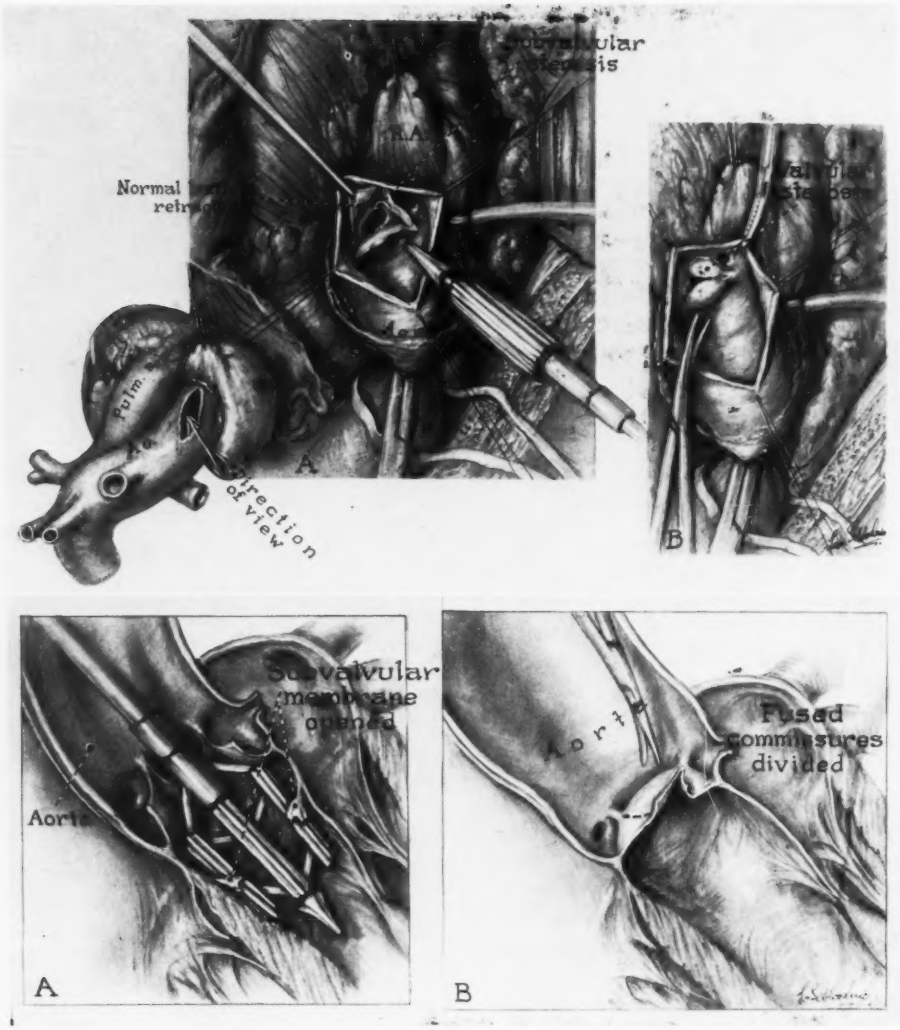
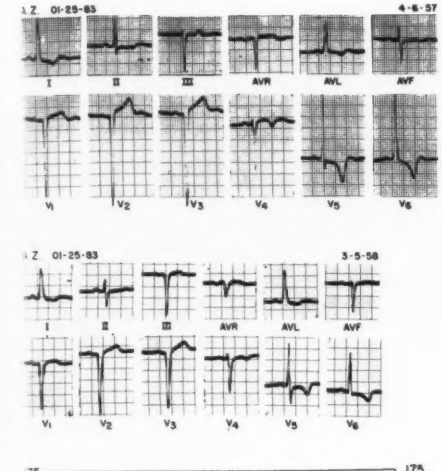


FIG. 5 *Top.* Subvalvular (*A*) and valvular (*B*) congenital aortic stenosis as seen in the course of operation under direct vision. *(Reproduced by permission from Progress in Cardiovascular Diseases* **1**: *80, 1958)*[5]

FIG. 6 *Bottom.* Operative management of subvalvular (*A*) and valvular (*B*) obstructions under direct vision. Subvalvular membrane is exposed by retraction of leaflets, and is cut and dilated.

(W. F.) who had significant pulmonary hypertension preoperatively, a right heart catheterization 9 months after operation revealed that all right heart pressures were normal.

Peripheral arterial pulse pressures were generally increased postoperatively. Three patients have abnormally low diastolic arterial pressures and the auscultatory findings of aortic regurgitation. Two of these patients (N. S. and E. R.) had aortic diastolic murmurs before operation but it is believed that the commissurotomy increased the pre-existing



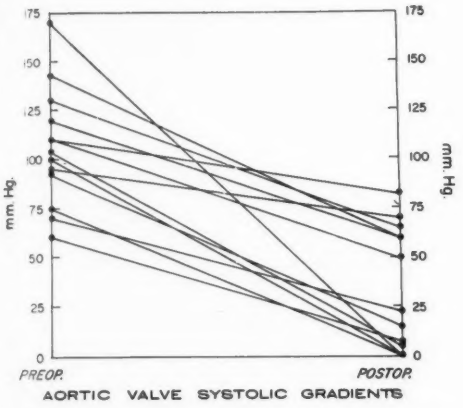


FIG. 7 *Top.* Electrocardiograms made before operation (*upper*) and 1 year after operation (*lower*) in patient A. Z. with subvalvular obstruction.

FIG. 8 *Bottom.* Aortic valve gradients before and after operation in the 13 patients in whom both measurements were made.

aortic regurgitation. The aortic regurgitant flows in these 2 patients were found postoperatively to be 4.7 and 1.6 L./min. respectively. In the other patient (G. G.) an aortic diastolic murmur was heard for the first time after operation. Patient R. R. had a grade II diastolic murmur, which was unchanged after operation. His postoperative regurgitant flow was estimated at 0.6 L./min. These patients are all asymptomatic although 1 (E. R.) has shown a slight increase in heart size roentgenographically.

DISCUSSION

There is now abundant evidence that congenital stenosis is a lesion that may pose a threat to life. In the present series, 2 patients (D. M. and J. R.) died suddenly on the ward while awaiting operation. Some observers have had similar experiences.[1-3] Hemodynamic evidences of severe outflow obstruction and elevated left ventricular filling pressure were frequent in the patients studied. Many patients in this and other series were severely incapacitated by angina, syncope, and dyspnea, and the incidence of sudden death has been estimated at nearly 10 per cent.[3] Subvalvular stenosis has, in particular, been regarded as a benign lesion, offering little obstruction to left ventricular outflow in the vast majority of cases.[17] Three of the largest aortic gradients in the present series, however, were recorded in patients with subvalvular obstruction and 2 of them were severely limited by angina and dyspnea.

The diagnosis of aortic stenosis is ordinarily apparent from the characteristic harsh systolic murmur and thrill at the base of the heart that are transmitted to the carotid arteries. The lesion may be considered congenital if the murmur is detected in infancy or in early childhood and if there is no evidence of other valve involvement or a history of rheumatic fever. Congenital aortic stenosis may be masked by the presence of associated anomalies, the most common of which are patent ductus arteriosus[18] and coaretation of the aorta. The chief value of right heart catheterization is in the detection of patent ductus and in the differentiation of aortic stenosis from ventricular septal defect or pulmonic stenosis. This technic is of little value in estimating the severity of the aortic lesion itself. With 1 exception the resting cardiac indices measured were within normal limits. It was of interest that no correlation existed between the aortic valve gradient and the resting cardiac output.

Subaortic stenosis has been considered to be a very rare congenital anomaly of the heart; a total of 45 cases had appeared in the medical literature before 1949.[17] It was

therefore of considerable interest that the obstruction was subvalvular in 8 of the 21 patients in whom the diagnosis was proved (at operation in 17 and by left heart catheterization in 4). The valvular and subvalvular form of congenital aortic stenosis, in the present series, could not be distinguished on the basis of clinical findings, electrocardiography, or standard roentgenographic technics. Poststenotic dilatation of the aorta was present in both groups. Intravenous or selective angiocardiograms with pulmonary artery injection were carried out in 11 of the patients in this series. In no instance could the site of obstruction be precisely located. Direct injections of contrast substances into the left heart have not been employed in patients with aortic stenosis in this clinic. The only method by which the site of obstruction could be localized before operation was transbronchial left heart catheterization. The presence of subvalvular stenosis was established in 4 of the 8 patients with this lesion when the catheter tip was withdrawn from the aorta through an area where the systolic pressure was equal to that in the aorta and the diastolic pressure was that of the main left ventricular chamber. In the other 3 patients with subvalvular stenosis in whom the transbronchial route was employed the catheter could not be manipulated into the aorta.

The incidence of aortic regurgitation among the patients with subvalvular obstruction is high. Aortic diastolic murmurs were present preoperatively in only 4 of the 13 patients with valvular stenosis, while 4 of the 8 patients with proved subvalvular obstruction had the murmur of aortic regurgitation. In 1 of the latter (H. L.) the presence of significant aortic reflux was proved preoperatively by an indicator-dilution technic.[11] When aortic valvular incompetence is encountered in association with a subvalvular membrane, its etiology must remain a matter for speculation. At operation the valve leaflets have frequently been noted to be thickened and fibrotic. This observation was further confirmed by the autopsy findings in patient H.L.; the leaflets were considerably thickened, their edges rolled, and they did not approximate centrally. Similar pathologic observations have been made by Burchell and Edwards, who attributed the valvular damage to the impact of the jet of blood from the subaortic orifice.[19, 20] Deformity of the valve may also result from a previous, unrecognized and healed bacterial endocarditis.[21] Edwards believes that this complication may also be related to the trauma of the jet impact on the valve.

Ideal management of the patient with congenital aortic stenosis requires an accurate estimate of the severity of the obstruction. In the present series prominent symptoms were always associated with severe hemodynamic alterations. On the other hand, both hemodynamic and anatomic evidence of severe obstruction was present in several patients who had not yet developed symptoms. In general, electrocardiographic evidence of left ventricular hypertrophy was accompanied by a large pressure gradient but exceptions to this were occasionally noted. Precise evaluation of the degree of obstruction to left ventricular outflow depends not only upon the measurement of the pressure gradient but also upon the simultaneous determination of blood flow across the aortic valve. The recent combination of the technics of left heart catheterization and measurement of cardiac output by the indicator-dilution method[9] has made possible the preoperative estimation of orifice size. Such measurements materially aid in the selection of patients for operation. It is currently the policy at the National Heart Institute to recommend operation to patients with congenital aortic stenosis who, regardless of symptoms, have aortic valve gradients in excess of 50 mm. Hg or calculated orifice areas less than 0.5 cm.^{2}/M.^{2} BSA. Further experience may indicate changes in these arbitrary standards.

Congenital valvular aortic stenosis is, in general, a more favorable anatomic lesion than acquired stenosis. Calcification may occur in the congenitally narrowed valve, and was present in the 5 oldest patients in this series. The transventricular and the closed transaortic technics for aortic valvulotomy seem particularly unsuitable for the treatment of

congenital stenosis, since accurate division of congenitally fused commissures would appear to be difficult without direct vision. This conclusion is borne out by the experiences of Marquis and Logan,[22] who reported severe aortic insufficiency in 4 of 6 patients operated upon through the left ventricle. Relief of subvalvular obstruction through an aortic pouch has not been reported and would seem to be difficult or impossible.

The open operation described provides excellent exposure of the valve and permits precise control of the commissurotomy. Complete anatomic correction with separation of the commissures to the annulus was at first attempted and was probably responsible for the development or aggravation of aortic insufficiency in some patients. At present the commissures are divided only partially and the valve is opened further by dilatation. The valve in 1 patient (G. G.) appeared to be bicuspid, and the possible occurrence of this variation must be borne in mind lest a leaflet be damaged in an attempt to open a nonexistent commissure. Among the 7 patients with subvalvular stenosis, the obstruction was due to a fibrous ring in 6; it was easily cut and dilated. In the other patient (A. Z.) a thick musculofibrous ridge occluded the outflow tract, and division and dilatation were carried out. In this instance, however, resection of the obstructing tissue might have been preferable.

Although most patients surviving operation have had gratifying clinical results, postoperative hemodynamic studies in all but 5 indicate that some degree of residual stenosis exists. The necessarily brief period allowed for visualization of the valve is the chief disadvantage of the open operation with hypothermia. A logical extension of the method has been the application of a similar technic during elective cardiac arrest or retroperfusion of the coronary arteries with circulatory support by means of extracorporeal circulation.[23, 24]

Summary

The clinical and hemodynamic findings in 30 patients with congenital aortic stenosis are summarized, and the potentially serious nature of this defect is emphasized. The use of left heart catheterization in the precise assessment of the severity of the obstruction and in the detection of subvalvular stenosis is described. Eighteen patients were operated upon, 14 with direct exposure of the aortic valve. The technic, advantages, and limitations of the open operation are discussed, and the clinical and hemodynamic findings in patients studied after operation are presented.

Summario in Interlingua

Es summarisate le constatationes clinic e hemodynamic in 30 patientes con congenite stenosis aortic. Es sublineate le potentialmente grave character de iste defecto. Es describite le uso de catheterismo sinistro-cardiac in le evalutation precise del severitate del obstruction e in le detection del presentia de stenosis subvalvular. Dec-octo patientes esseva operate, 14 con exposition directe del valvula aortic. Le technica, le avantages, e le limitationes del operation aperte es discutite, e le constatationes clinic e hemodynamic in patientes studiate post le operation es presentate.

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TRUTH AND LIBERTY

John Milton
English Puritan poet, 1608-1674

Where there is much desire to learn, there of necessity will be much arguing, much writing, many opinions; for opinion in good men is but knowledge in the making.—*Areopagitica.* From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

Use of Biplane Cinefluorography for Measurement of Ventricular Volume

By Carleton B. Chapman, M.D., Orland Baker, M.D., Jack Reynolds, M.D., and Frederick J. Bonte, M.D.

A biplane cinefluorographic technic for measuring ventricular volume is described and its accuracy and limitations are assessed. Although rather complicated and time-consuming at present, the method permits construction of volume curves and estimation of stroke volume of the left ventricle for several successive contractions in the intact animal or man. This method may prove most useful for physiologic research and ultimately for diagnostic purposes.

THE lack of a means of following change from instant to instant in left ventricular volume in the intact animal constitutes a major technologic barrier to further advance in mammalian cardiovascular physiology. An approach to this problem has been made, both in the dog and in the human being, utilizing biplane cinefluorography. The following account describes the method and the mathematical treatment needed to convert biplanar ventricular images to 3-dimensional ones.

Background

The photographic method itself is old. The moving-picture technic was demonstrated in satisfactory form for the first time in 1889, 6 years before Röentgen discovered x-rays. In 1897, when neither moving pictures nor x-rays had widespread application, MacIntyre[1] attempted to combine the 2 technics so that a continuous record of the movement of internal organs could be obtained. Eykman[2] was the first to use a movie technic for studying the motion of the heart, although Groedel[3] was experimenting with serial roentgenography for the same purpose at about the same time. Indirect cineroentgenography, in which a fluoroscopic screen is photographed rather than causing x-rays to impinge directly on photographic film) was accomplished by Loman and Comandon[4] in 1911. They recognized many of the difficulties that persist to this day, but were able to photograph the movement of a monkey's heart at 8 to 10 frames a second. In 1926, Chamberlain and Dock[5] used a form of roentgencinematography for the study of the heart. Later, Luboshez[6] improved the optical systems in cinefluoroscopic units. Further improvements followed,[7–10] and shortly after World War II, an improved 35 mm. cinefluorograph was developed.[11–13]

Efforts to determine cardiac volume from single x-ray films go back at least to the turn of the century,[14] but the first equations for calculating cardiac volume from x-ray films (orthodiagrams) were devised by Geigel[15] in 1914. His prime assumption was that the heart can be treated mathematically as a sphere:

$$V = \frac{4F3/2}{3}$$

where

V = volume
F = largest diameter in posteroanterior plane

Somewhat later, Bardeen[16] evolved a similar equation in which the area of the frontal silhouette, instead of its broadest diameter, was employed. The method, based on measurement of 62 hearts at autopsy, was said to permit calculation of diastolic volume to within 5 per cent.

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Probably the most significant of the earlier attempts of this sort was Rohrer's.[17] He assumed that the volume of a body of any shape is equal to the area of its projection times the mean diameter of the projection. In actual practice he used the area of the frontal projection of the heart (F), and the largest diameter in the lateral projection (L) multiplied by a constant. His equation was

$$V = 0.63\ FL$$

Later, Kahlstorf[18] noted that the volume of an ellipsoid is 0.66 FL, while the volume of a paraboloid is 0.59 FL. Since the heart is neither an ellipsoid nor a paraboloid, the necessary factor must lie between these 2, and Kahlstorf finally reached the equation suggested earlier by Rohrer. He, like Bardeen, found a 5 per cent error when he tested the equation on 13 hearts at autopsy.[19] Relatively slight modifications, with 3 separate diameters (instead of an area and 1 diameter)[20, 21] and other technics requiring the construction of models of the heart from numerous fluorographic views of the organ, were also suggested.[22]

A significant modification, involving 2 simultaneously recorded views,[10] served as the basis for important and often quoted Scandinavian studies on cardiac volume under various physiologic conditions.[23, 24] More recently, Soloff and co-workers[25] applied a biplane angiocardiographic method, providing an exposure every 0.7 second, to estimate left atrial volume.

For physiologic purposes, the main deficiencies of the methods as developed to this stage were that total heart volume, rather than intracavitary ventricular volume, was approximated; also, sequential measurements for construction of ventricular volume curves were not provided. The technics did not, in fact, offer much assurance that diastolic and systolic volumes could be readily distinguished. For these reasons, a combined movie-x-ray technic for quantitative, physiologic purposes was inevitable. One of the first attempts was made by Timm[26] who used cinematic technics in animals for studies of the movement of blood in the aorta in 1944. A similar technic (single plane) was used somewhat later by Gauer in studies of left ventricular volume.[27] Cinefluorographic methods, at rates up to 30 frames a second, were used in studies of ventricular function by Rushmer and Thal in 1950.[28] They did not attempt to calculate volume as such, but used ventricular area in a single plane as an index to volume. Somewhat similar methods were used by Reynolds et al.,[29] in studies of blood flow in umbilical vessels.

The next logical step in the development of a method for following change in ventricular volume seemed to be the construction of a biplane cinematic x-ray device capable of recording ventricular images at high rates of speed. With such records in hand, it was thought that a mathematical method for converting biplane ventricular images to volume in absolute units might be worked out.

The Instrument

Two complete 35-mm. cinefluorographic units, of the type described by Ramsey and colleagues, were built for biplane operation. The cameras are housed in light-tight boxes, each having a 15 by 15 inch Patterson CB-2 fluorescent screen at the end facing the x-ray tube, the camera itself being at the other. A bellows connection between the 2 ends permits adjustment for field size up to 13 by 15 inches. The camera units are mounted on supporting carriages equipped with heavy casters, making positioning simple and precise. Each fluorescent screen is provided with a fine-line grid, permitting tube-to-screen distances of 26 to 32 inches. A Wray (London) 64 mm. f/0.71 lens focuses the image of the fluorescent screen on the film. Counter-rotating shutters, driven by timing belts directly from the film transport mechanism, cut off image persistence from the screen and prevent fogging during transport of the film.

The film transport mechanism is driven through an adjustable gear train by a 1/3 h.p. synchronous motor. A commutator, which is also driven by this gear train, energizes the x-ray tube only when the film is

correct position for exposure. The arrangement makes synchronous biplanar images possible at rates from 3¾ to 30 frames per second. At 30 frames per second, each frame is actually exposed to 2 firings, 1/120 second apart; each tube, after firing twice, then rests for 1/60 second. The design of the instrument is such that the 2 tubes sometimes fire asynchronously, one leading the other by precisely 1/60 of a second. For this reason, special warning circuits are provided so that if asynchronous firing occurs, the tube that fires first can be identified.

The controls for both units are housed behind appropriate shielding and permit independent settings to be made on each unit as required. Settings can be made up to 130 kv. and 200 ma. on each machine. Maximal continuous cinematic exposure time at these settings is 6 seconds (30 frames per second) with a proportionate increase in exposure time as the tube load is decreased.

Tube firings are delayed about 2 seconds after the camera motors are started in order to permit the motors to gain momentum and to run synchronously.

In order to determine the ability of the camera to stop rapid motion, a metal disk with holes punched at varying radii from the center was rotated in front of the camera. With the r.p.m. and distance of each hole from the center of the disk known, the linear velocity at which blurring occurred could be calculated. At a velocity of 90 cm. per second, motion was stopped completely; at 110 cm. per second, slight haziness of the leading and trailing edges of the holes could be perceived, and at 130 cm. per second definite blurring occurred.

The Method

In order to arrive at a method of calculating ventricular volume from biplanar cinematic images, experiments were devised with ventricular models and with intact dogs. The models were of several varieties. Initially, a radiopaque sphere was used; next a metal cylinder fitted, at one end, with a conical cap (fig. 1) was tried. Both models were hung in front of the cameras (placed at 90 degrees to each other) and were rapidly spun as photographs were made. Rough models of the left ventricular cavity were then made in 12 different sizes. Each was suspended before the cameras and photographed simultaneously in 2 planes. Volumes of models were calculated from the films and the results were compared to those obtained by a displacement technic. Finally, the same method was used to measure the volumes of actual casts of the canine left ventricular cavity.

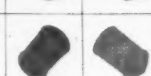
FRAMES	CAMERA		VOLUMES (CC.)		
	1	2	Actual	Simpson's Rule	Area Products
7			179	154	130
11			179	190	145
18			179	196	153
23			179	198	155

FIG. 1. X-ray photographs of a metal cylinder capped with a cone and spun rapidly before the 2 cameras. Pairs of frames (7, 11, 18, and 23) show position of the model at various points in its cycle as seen by the 2 cameras. Volume calculations by 2 methods and actual volume are shown at right.

Left ventricular function in the living animal was studied in mongrel dogs, weighing from 10 to 15 Kg. After anesthesia with intravenous sodium pentobarbital and endotracheal intubation, an injection cannula was placed in the inferior vena cava or in the pulmonary artery. A smaller catheter was passed from the femoral artery into the aortic arch for recording of aortic pressure. In a few instances a short PE-90 catheter was passed through the chest wall directly into the left ventricle by means of a thin-walled 16 gage needle. The dog was suspended before the cameras by means of a special body sling in as natural a position as possible. The optimal position for biplanar visualization of the dog's heart provides right and left anterior oblique views of very satisfactory quality, provided the forelegs and scapulae are drawn well out of the way.

Once the animal was in position, the injection catheter was connected to a Rodriguez-Chavez Dorbecker type of pneumatic injection machine* loaded with 15 to 20 ml. (0.5 ml. per Kg.) of a 90 per cent solution of diatrizoic acid salts (Hypaque-M). The arterial and ventricular cath-

*Manufactured by the Presojector Manufacturing Company, Fort Worth, Tex.

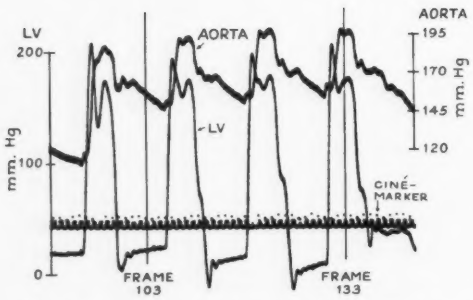


FIG. 2. Aortic and left ventricular pressure tracings, and cinematic marker indicating precise instants at which numbered film frames are exposed. The space between vertical lines marked frame 103 and frame 133 represents 1.0 second.

eters were attached via strain gages to an electronic photographic recorder. The response characteristics of the several systems of pressure recording depend mainly on the catheters used. When a No. 6 or 7 catheter 100 cm. long was employed, the natural frequency (without mechanical damping) was about 7 c.p.s. When a PE-90 catheter 45 cm. long was used, the natural frequency was 22 c.p.s. When a double-lumen catheter for recording left ventricular and aortic pressures was used, natural frequencies were 7 (ventricular) and 11 (aortic) c.p.s. (fig. 2). A monitoring circuit from the primary winding of the x-ray transformer, also feeding into the recorder, was arranged so that the instant at which one of the x-ray tubes fired was signalled on the pressure record (fig. 2).

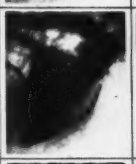
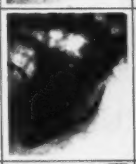
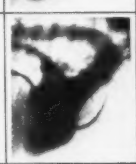
The usual x-ray settings for the dog studies are 120 kv. and 150 ma. at 30 frames per second. Film records usually extend over 6 to 10 seconds, care being taken to obtain the desired temporal relation between injection of radiopaque medium and the beginning of the film record.

The usual x-ray settings for a human subject are 126 to 130 kv. and 150 ma. for a 4 to 6 second run. For somewhat greater than average bodily dimensions, maximal settings of 130 kv. and 200 ma. are used. Thick-chested individuals are difficult to photograph, even at maximal settings, and in such cases ventricular contours are too indistinct to permit accurate tracings, although the films are adequate for diagnostic purposes.

In order to gage the radiation dosage delivered by the biplane unit to human subjects, measurements were made in air at skin distance from each tube. The dosage at 200 ma. and 130 kv. for a 6 second run at 30 frames a second with no filter was 37 roentgens from the posteroanterior tube and 74.5 roentgens from the lateral tube. With a 2 mm. aluminum filter the tube dosage was 20 and 39.5 roentgens, respectively. With 2 mm. aluminum and 0.25 mm. copper filters, the dosage was further reduced to 9 and 17 roentgens. The filters impair definition of images remarkably little and, because of the high radiation administered when they are not employed, are essential for human work. Because of the radiation hazard, runs are repeated on human subjects only if they are essential for diagnostic purposes. For the same reason, the technic is not currently being used in children.

To visualize the human left ventricle, a no. 9 birdseye-tip cardiac catheter is first placed in the pulmonary artery by the usual right heart catheterization technic. To record aortic pressure, a no. 5 birdseye-tip catheter is passed via the brachial artery to a point just proximal to the origin of the innominate artery. The subject is then transferred by wheel chair to the cineangiofluorography room and is seated in front of the cameras, the precise positioning depending on what portion of the heart is to be visualized. For the left ventricle, modified left lateral and right anterior oblique views have proved most suitable; the former is approximately 10 degrees anterior to a left lateral view, the latter approximately 25 degrees to the right of a posteroanterior view. The cameras are positioned so that the screens form an angle of about 75 degrees instead of the 90 degree angle usually used with dogs. The subject's arms are placed on top of the fluoroscopic screens, well out of the field, to facilitate connection of the catheters with the injector and strain gages. An 80 cm. length of large caliber (3.5 mm. inside diameter) thick-walled polyethylene tubing, fitted with Luer-Lok adapters, forms a connection between the injector stopcock valve and the pulmonary artery catheter. A Statham transducer is connected directly to the aortic catheter for pressure measurement.

The injector is then filled with radiopaque medium (30 to 40 ml.). With the stopcock closed, a pressure of 70 pounds per square inch is applied to the pneumatic cylinder. In order to minimize x-ray exposure, injection is carefully timed, depending on the chamber of the heart to be visualized. For the left ventricle, with injection into the pulmonary artery, the cameras are started so that photography begins about 2 seconds after injection. The injector delivers 50 ml. of contrast medium through a no. 9 catheter in 1.7 seconds. For 15 minutes prior to injection, and during the cinematic run itself, intermittent positive pressure breathing with 100 per cent oxygen is instituted in order to attain maximal oxygenation and to minimize the hazard of dye injection. The typical reaction to the injection under these circum-

Frame	RAO	LAO	X (RAO x LAO) Sq. cm.	Y (VOL. IN CC.) From Area Products*
176			19.5 x 19.0	55.6
177			19.9 x 19.0	56.6
178			20.8 x 20.2	61.6
179			22.3 x 20.9	66.9
180			23.1 x 21.5	70.5
181			24.0 x 23.2	77.3
182			25.0 x 24.1	83.9

* Log Y = −0.3256 + 0.8062 Log X

FIG. 3. Left ventricular cycle, beginning at the end of systole (frame 176) as seen in 2 planes, with volume as calculated by the area product method.

stances is flushing and, a few seconds later, coughing and occasionally vomiting. Still later, there is a temporary slight decline in aortic pressure, but in about 40 injections into human subjects, no serious reactions have been encountered.

Once a run is completed, the film is promptly developed and inspected while still wet. If it is unsatisfactory, or if additional runs are desirable for some other reason, second and third films can be made (in dogs) without difficulty. When film-

Frame	RAO	LAO	X (RAO x LAO) Sq. cm.	Y (VOL. IN CC. From Area Products
183			25.7 x 24.6	85.6
184			26.3 x 25.8	90.6
185			26.2 x 25.2	88.6
186			21.5 x 20.9	65.0
187			20.2 x 20.1	59.7
188			20.5 x 19.7	59.7

* Log Y = −0.3256 + 0.8062 Log X

FIG. 4. Completion of the cycle, beginning with maximal filling (frames 183 and 184) and continuing almost to the end of systole.

ing is finished, the approximate position of the subject's heart before the cameras is determined and the subject is removed. A lead reference standard is then suspended in the position previously occupied by the heart and a short film record of it is made. Finally, 16 mm. positive prints are made from the 35 mm. negative strips.

The most laborious part of the procedure [illegible] follows. Twin 35 mm. still projectors are set [illegible] side by side so that the projected image is [illegible] flected by front-surface mirrors without disto[illegible] or loss of clarity onto a horizontal surface be[illegible]. The height of the projectors is adjusted so [illegible] the filmed images of the reference standard c[illegible]

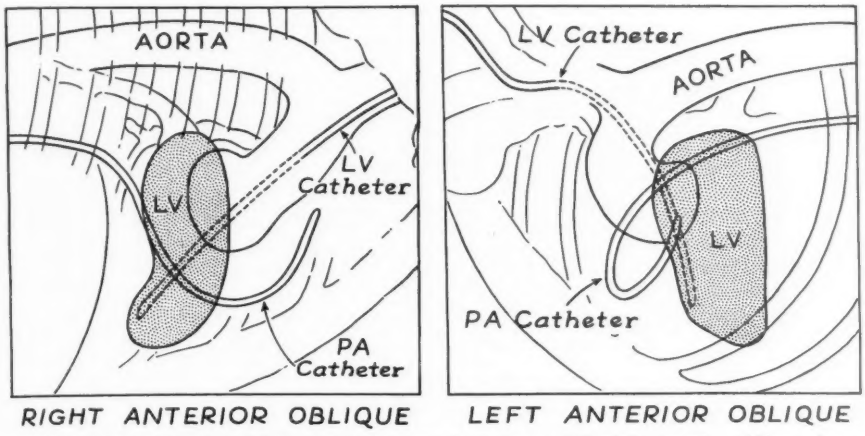


FIG. 5 *Left.* Tracing of left ventricular area from frame 176, right anterior oblique view.

FIG. 6 *Right.* Tracing of left ventricular area from frame 176, left anterior oblique view.

sponed precisely in size to the actual standard. This maneuver minimizes the distorting effect of diverging x-rays and insures that the projected image is very close in area to that of the original object. Each of the simultaneously recorded 35 mm. film strips is then numbered (every tenth frame) and put into one of the 35 mm. still projectors. Two operators, one for each view, trace corresponding frames simultaneously, frequently comparing shapes and boundaries as they proceed. A 16 mm. movie projector, loaded with a loop of the appropriate 16 mm. reduction print (both views) is placed so that both operators can view the movie version, as well as the still, conveniently and frequently. Figures 3 and 4 show consecutive biplane frames of the canine left ventricle as they appear when the 16 mm. movie film is projected. The importance of using the movie version as a reference while the stills are being traced cannot be overemphasized. Without it many obscure lines and borders are either misplaced or overlooked entirely. This is especially true of valve planes. Figures 5 and 6 show left ventricular tracings from frame 176 of the film depicted in figure 3.

In the case of the left ventricle, the aortic valve plane, aortic bulb, and aortic diameter just above the bulb are routinely indicated on the individual tracings. The tracings are then arranged in numerical order and left ventricular areas in each plane are determined planimetrically. Aortic diameters (just above the bulb) are measured and recorded. Finally, the ventricular tracings are oriented on the surface of an illuminated view box over a 1 mm. horizontal grid. Diameters from top to bottom of each ventricular tracing are then measured at 1 mm. intervals (fig. 7).

Measurement of pressure tracings is carried out by construction of perpendicular lines corresponding to the marks recorded with each firing of the x-ray tubes. The points at which the lines intersect the pressure tracing are then measured and converted to mm. Hg by use of a conversion factor derived from the calibration record made after each run. The operation provides the aortic or ventricular pressures that prevailed as each 35 mm. frame was exposed.

CALCULATIONS

The method of measuring left ventricular volume from 2 simultaneously recorded plane figures rests on the assumption that the cross-sectional outline of the ventricle is elliptical or circular, and that the 2 figures record a major and a minor axis of the ellipse. These assumptions, in the case of the left ventricle, are not unreasonable, but cannot be applied to the right. Figure 7 shows the application of this reasoning to the problem at hand. Each plane figure is split into cross sections 1.0 mm. thick. The volume of each cross section is obtained by multiplying the area of the elliptical figure by its thickness:

$$V = \frac{\pi h (AA \times BB)}{4}$$

where

H = thickness (1.0 mm.)

AA = diameter in left anterior oblique view at a certain level (fig. 7) in mm.

BB = diameter in right anterior oblique view at same level as AA (fig. 7) in mm.

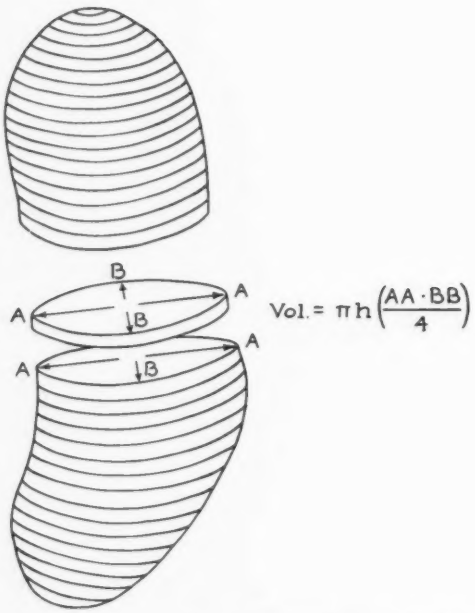


FIG. 7. Diagram of left ventricular cavity, showing method of calculating volume from 2 diameters (AA and BB).

Summing the cross sectional volumes provides an estimate of the volume of the entire ventricular chamber at a particular instant in time. The thinner the slices, the more accurate is the estimate. The basic principle is the same as that embodied in Simpson's Parabolic Rule. As used for present purposes, the equation is:

$$V = \frac{\pi h}{3}\left((\Sigma D_{RAO_O} \times D_{LAO_O} + \frac{(\Sigma D_{RAC_E} \times D_{LAO_E})}{2}\right)$$

where

h = 1.0 mm.

D_{RAO_O} = right anterior oblique diameter of odd sections in mm.

D_{LAO_O} = left anterior oblique diameter of odd sections in mm.

D_{RAO_E} = right anterior oblique diameter of even sections in mm.

D_{LAO_E} = left anterior oblique of even sections in mm.

The tedium of the method as outlined is made apparent by the fact that, for a single run, it is necessary to trace out 200 to 600 frames (100 to 300 in each of 2 views); then, one must measure diameters from each image

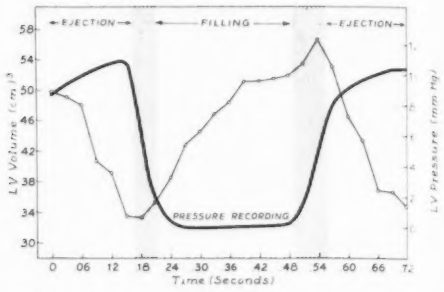


FIG. 8. Ventricular pressure and volume curves in normal dog (see table 1).

at 1 mm. intervals. Each image usually contains 40 to 60 diameters, so that upward of 25,000 diameters may have to be measured for a single run. In order to eliminate some of this drudgery, the relation of the product of the areas (right anterior oblique and left anterior oblique), as measured planimetrically, to the volume, as obtained using the modified Simpson's Rule, was scrutinized. Several empirical equations were obtained to express this relation, which appears to be parabolic rather than linear. For example, in the case of the dog heart, the relation is:

$$\text{Log } Y = -0.3256 + 0.8062 \text{ Log } X$$

where

Y = volume in cm.^{3}

X = product in cm.^{4} of areas in cm.^{2}

Other equations are applicable to models and to larger mammalian hearts, including the human. Use of the equations still requires planimetric measurement of 2 ventricular areas for each 1/30 second time interval but is much less time-consuming than use of the modified Simpson's Rule technic.

Plotting of ventricular volume curves from such data is then a simple matter; there are usually 15 to 25 points in each cycle (dog) depending on the pulse rate (fig. 8, table 1). One can also derive ejection increments and, by calculating corresponding aortic areas (from 2 aortic diameters measured immediately above the aortic bulb), aortic velocity for each 1/30 second interval can be obtained. The volume used in the calculation is derived by plotting an actual ejection

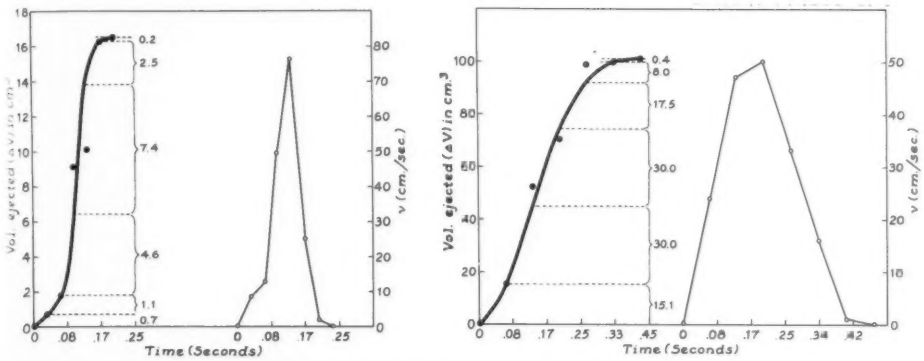


FIG. 9 *Left.* Ejection and velocity curves in normal dog.

FIG. 10 *Right.* Ejection and velocity curves in normal human subject.

curve (figs. 9 and 10), drawing a smooth line between them, and noting points on the smoothed curve corresponding in time to the observed volumes. ΔV is taken as the volume change between successive marks. Velocity in cm./sec. is calculated by dividing ΔV by the appropriate aortic cross sectional area in cm.^{2}

RESULTS

Model Experiments

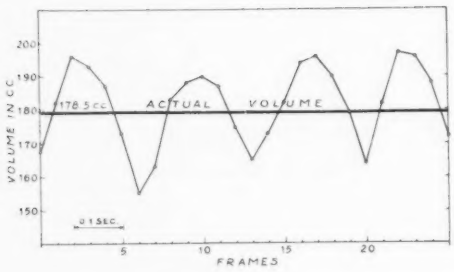
The diameter of the radiopaque sphere was 5.6 cm. and its calculated volume was 92 cm.^{3} As determined from the films by the Simpson's Rule method, its volume was 91.5 cm.^{3}, a very close approximation to the calculated volume.

Results of studies on the schematic model of the left ventricle are shown in figures 1 and 11. The volume of the model, as calculated from its various dimensions, was 171.3 cm.^{3}, and that determined by displacement was 179 cm.^{3} In figure 1, sample pairs of frames, taken as the model was spinning clockwise in front of the 2 cameras, are shown. The area product method appeared to underestimate the volume, probably because no suitable equation was available. Volumes determined by the Simpson's Rule method, however, show a regular waxing and waning above and below the actual volume (fig. 11). The geometric reasons for the phenomenon can be deduced from figure 1. Percentagewise, the method yields values that vary from a 10 per cent overestimate to a 13 per cent underestimate, depending on the spatial relation of the model to the 2 cameras at any particular instant. It will also be apparent that spinning the model through 360 degrees constitutes a very severe test, in one sense, for the

TABLE 1.—*Data Obtained from Pairs of Frames (271-287) for Calculation of Ventricular Volume in the Normal Dog through One Complete Cycle*

Frame	Area (cm.^{2})		Volume (cm.^{3})			
	Right anterior oblique	Left anterior oblique	Area products (cm.^{4})	Simpson's Rule	Regression equation*	Pressure (mm. Hg)
271	17.5	17.8	312	49.8	48.4	87.2
272	17.8	17.2	306	49.1	47.8	93.6
273	18.0	16.7	301	48.0	47.2	99.3
274	16.8	15.0	252	40.7	41.8	103.5
275	16.4	14.8	243	39.1	40.8	107.8
276	14.5	13.1	190	33.5	34.5	107.8
277	13.6	12.8	174	33.3	32.5	58.1
278	14.5	13.6	197	35.4	35.3	19.1
279	15.1	14.6	221	38.5	38.2	3.5
280	15.8	15.8	250	42.8	41.5	0.0
281	16.7	16.2	271	44.5	43.9	0.0
282	17.8	16.4	292	46.9	46.3	0.0
283	17.8	16.9	301	48.4	47.2	0.0
284	19.0	17.4	331	51.2	50.4	0.7
285	18.2	17.2	313	51.2	48.5	1.4
286	18.8	16.8	316	51.6	48.8	1.4
287	18.6	17.2	320	52.0	49.2	1.4

*Log $Y = -0.3256 + 0.8062$ Log X.



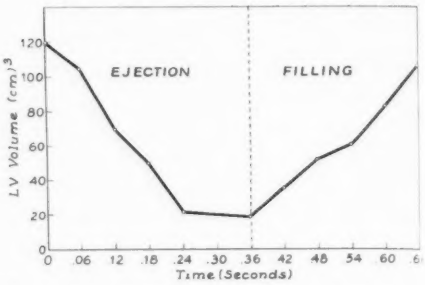


FIG. 11 *Left.* Oscillation of model volume (fig. 1) calculated by the Simpson's Rule method from biplane films, around the actual volume.

FIG. 12 *Right.* Ventricular volume curve in normal human subject.

method; the left ventricle in the intact animal oscillates with each beat along a small arc but does not rotate through a full circle.

Data obtained by photographing plaster models shaped to resemble the actual left ventricular cavity are shown in table 5. Each of the first 6 models was photographed in 3 different positions (but not moving) for reproducing something of the cyclic change in orientation characteristic of the intact left ventricle. It will be seen that the area product method tended to overestimate volume, its error ranging from +13.0 to −15.4 per cent (mean +2.5 per cent). Simpson's Rule produced values that were as much as 13.8 per cent above, and 11.6 per cent below, the actual value. The mean deviation, however, is slightly lower than that for the area product method (1.4 per cent). Both methods, in this experiment, appear to measure the same variable with about equal facility, the Simpson's Rule method giving a slightly better performance than the area product one.

In the case of the cast of a canine left ventricular cavity, both methods produced overestimates of volume, the area product method being the more inaccurate. Since the heart was a small one (17.5 cm.³ as determined by displacement), it may be that the equation used was inapplicable. The material from which it was derived consisted of a series of living canine hearts, all larger than the one used for the cast. In any case, area product volumes were too high as compared to actual volume, but the area product volume curve

TABLE 2.—*Data Used for Calculation of Velocity during Ejection Beginning with Frame 111. Normal Human Subject Filmed at 15 Frames a Second*

Frame	Aortic diameter (cm.) Left anterior oblique	Aortic diameter (cm.) Right anterior oblique	Cross-sectional aortic area (cm.²)	Volume (cm.³)	Velocity (cm./sec.)
111	3.10	3.50	8.87	—	—
112	3.45	3.40	9.25	15.1	24
113	3.40	3.48	9.55	30.0	47
114	3.30	3.78	9.05	30.0	50
115	3.25	3.25	7.89	17.5	33
116	2.90	3.28	7.56	8.0	16
117	2.80	3.48	7.72	0.4	1
118	3.00	3.30	7.58	—	—

TABLE 3.—*Data Obtained from Pairs of Frames (112-123) for Calculation of Left Ventricular Volumes in Normal Human Being through One Complete Cycle. Fifteen Frames a Second*

Frame	Areas (cm.³) Left anterior oblique	Areas (cm.³) Right anterior oblique	Area products (cm.⁴)	Volume (cm.³) Simpson's Rule	Volume (cm.³) Regression equation*
112	33.3	39.6	1318.7	120	132
113	32.2	37.9	1220.4	105	124
114	28.0	23.9	669.2	69	75
115	23.4	20.6	482.0	50	58
116	9.6	15.0	144.0	22	21
117	8.6	12.7	109.2	20	17
118	9.4	12.1	113.7	19	18
119	12.9	14.5	187.1	35	26
120	19.6	20.4	399.8	52	49
121	22.5	23.1	519.8	61	61
122	28.6	26.8	766.5	83	84
123	30.8	32.9	1013.3	106	96

*Log $Y = -0.4444 + 0.8216$ (Log X)

closely paralleled the Simpson's Rule volume curve. When the cast was spun before the cameras through 360 degrees, a mean value of 19.9 cm.^{3} was obtained, an error of about 1 per cent ($N = 33$). As with the schematic model, volume seemed to show a regular waxing and waning as the model spun, but the lowest volume recorded was 18.0 cm.^{3}

Volume Studies in Intact Dogs and Human Subjects

Estimates of left ventricular volume through 1 cardiac cycle are given in table 1 and figure 8. In this instance, both methods gave almost identical results. There is, however, no absolute measurement one can use for comparison. If, as may well be the case, the volumes are overestimated, it seems likely from the model studies that the overestimate is a systematic one and that the qualitative sequence of volume change is more or less correctly depicted.

Normal human left ventricular volume, ejection, and velocity curves are shown in figures 10 and 12 and are based on data set out in tables 2, 3, and 4.

TABLE 4.—*Data Used for Calculation of Velocity during Ejection Portion of Cycle Beginning with Frame 270*

Frame	Aortic diameter (cm.) Right anterior oblique	Aortic diameter (cm.) Left anterior oblique	Cross-sectional aortic area (cm.^{2})*	Volume (cm.^{3})	Velocity (cm./sec.)†
270	1.70	1.75	2.34	—	—
271	1.80	1.75	2.47	0.7	8.5
272	1.75	1.90	2.61	1.1	12.6
273	1.87	1.90	2.79	4.6	49.5
274	1.95	1.90	2.91	7.4	76.3
275	2.00	1.93	3.03	2.5	24.8
276	1.90	1.92	2.87	0.2	2.1
277	1.90	1.90	2.84	—	—

*Cross-sectional area of aorta is measured about 1 cm. above the plane of aortic valve.

†Velocity measurements refer to the interval of time *between* 2 frames, e.g., the first value 8.5 cm./sec. is the mean velocity prevailing in the time interval between frames 270 and 271.

Discussion

The development of more refined cinematic x-ray equipment has made it possible to follow the motion of the heart more minutely than was previously the case. The method may also be used to follow change in left ventricular volume although at present it is very tedious. Experiments with models show that volume of stationary objects shaped something like the left ventricle can be measured with reasonable accuracy. In the case of the living, beating left ventricle, validation becomes much more difficult largely because there is no other precise means of measuring stroke volume in the intact animal. Use of conventional technics of measuring minute volume, and dividing by the pulse rate, is hardly justified for purposes of comparison, since stroke volume does not necessarily remain constant from beat to beat.

The errors that are apparent in the method are several. The conditions under which the method must be applied depart from the physiologic in that dogs (but not human beings) must be anesthetized, and catheters for injection of contrast medium and for pressure measurements must be inserted. The contrast medium itself tends to cause a progressive lowering of aortic pressure after the first few strokes, either as a consequence of a direct effect on the myocardium or because of an effect on the peripheral arterial system, or both. Also, the relatively sudden arrival of increased fluid volume at the ventricle undoubtedly influences its power output. In spite of these objections, however, the technic simulates physiologic conditions more closely than do technics requiring opening of the chest, use of cardiometers, and direct insertion of aortic and venous cannulas.

The error in the method, as judged by experiments with ventricular models, is relatively small. With use of the modified Simpson's Rule equation, the method overestimated volume by an average of 1.4 per cent, but might, once in 20 tries, overestimate it as much as 16 per cent, or underestimate it as much as 13 per cent.

In the case of the intact left ventricle, some overestimation of volume is likely, but no precise measure of the error is available. It is

TABLE 5.—*Data Obtained from Photographs of Plaster Models*

Model No.	View*	Volume (cm.³)† Actual volume	Area product	Per cent deviation from actual	Simpson's Rule (vol. cm.³)	Per cent deviation from actual
1	a	274.0	286	+4.5	279	+1.6
	b	274.0	305	+11.4	312	+13.8
	c	274.0	257	—6.3	295	+7.7
2	a	258.0	267	+3.4	232	—10.1
	b	258.0	252	—2.5	257	—2.7
	c	258.0	260	+0.7	280	+8.5
3	a	235.0	262	+11.3	228	—2.9
	b	235.0	263	+11.9	237	+0.6
	c	235.0	202	—14.1	232	—1.2
4	a	183.0	187	+2.2	162	—11.6
	b	183.0	176	—4.2	164	—10.7
	c	183.0	181	—1.3	194	+5.9
5	a	140.0	145	+3.9	129	—7.6
	b	140.0	137	—2.4	144	+2.8
	c	140.0	137	—1.9	152	+8.6
6	a	63.5	71	+11.2	60	—6.1
	b	63.5	69	+9.0	65	+2.0
	c	63.5	63	—0.8	64	+1.4
7	—	62.0	68	+9.7	66	+6.3
8	—	57.0	48	—15.4	52	—8.6
9	—	47.5	51	+6.0	51	+5.4
10	—	46.0	52	+13.0	51	+10.9
11	—	43.0	43	—0.5	46	+5.8
12	—	38.0	42	+10.8	43	+12.9
Mean				2.5±7.8		1.4±7.4

*Model numbers 1-6 were oriented in 3 different ways: view *A* with apex hanging straight down; view *B* with the apex tilted up 30°, and view *C* with the apex tilted up and model rotated 45° counterclockwise with respect to positions *A* and *B*. Models 7-12 were oriented in a single position only.

†A comparison was made between volumes calculated by Simpson's equation and by a regression equation as compared to actual volumes measured by displacement technic. Per cent deviations are also shown.

clear, however, that the method accurately determines the beginning and end of ejection, that it follows the course of ventricular contraction and relaxation reasonably well, as judged by simultaneously recorded ventricular and aortic pressure curves, and that it is able to indicate even relatively small changes in end-diastolic and end-systolic volume with fair accuracy. These features, and the fact that the method can be applied to the intact animal or human being, justify the expectation that the method will prove to be an extremely useful one. Technical improvements such as faster camera speeds, suitable image intensification, and better contrast medium may confidently be expected. Lessening of the tedium now inherent in the method is also likely. While no suitable substitute for expert tracing of individual ventricular contours, frame by frame, is immediately foreseeable, electronic methods for measuring diameters of the tracings at 1 mm. intervals and completing calculations of volume by the Simpson's Rule equation are under development. Use of such a device will remove the most tedious and time-consuming feature of the method as it is now constituted.

SUMMARY

A biplane cineroentgen method of following change in volume of the left ventricle has been developed. Filming at the rate of 30 frames per second after rapid injection of radiopaque medium provides a series of ventricular images that are traced, frame by frame. Major and minor axes of the tracings are then measured at 1 mm. intervals and volume is calculated by use of a modified Simpson's Rule equation.

It is possible to use the method for measuring left ventricular stroke volume for each of several successive ventricular contractions. It also provides left ventricular volume and aortic velocity curves. The method is applicable to intact animals and human beings.

ACKNOWLEDGMENT

The invaluable assistance of Miss Martha Carver, x-ray technician, is gratefully acknowledged.

SUMMARIO IN INTERLINGUA

Esseva disveloppate un methodo de cineroentgenographia biplan pro observar alterationes de volumine in le ventriculo sinistre. Per facer le expositiones a un rapiditate de 30 per secunda, post le rapide injection de substantia radio-opac, on obtene un serie de imagines ventricular que pote esser tracate le un post le altere. Le axes major e minor del traciamentos es alora mesurate a intervallos de 1 mm, e le volumine es calculate per le uso de un modificate regula de Simpson.

I es possibile usar le methodo pro mesurar le v lumine per pulso sinistro-ventricular pro cat un de plure successive contractiones ventri lar. Illo etiam provide curvas de volumi sinistro-ventricular e de velocitate aortic. Le methodo es applicabile a intacte anima s e humanos.

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Radioactive Fat Absorption Patterns

Their Significance in Coronary Artery Atherosclerosis

By William Likoff, M.D., Donald Berkowitz, M.D., Asher Woldow, M.D., A. Gerson Jacobs, M.D., and David M. Sklaroff, M.D.

Fat tolerance tests with radioactive triolein were performed on a group of patients with coronary atherosclerosis or hypercholesterolemia, and significant differences from normal subjects were observed. The mechanisms and implications of these abnormalities are discussed.

ATHEROSCLEROSIS and its accompanying vascular lipoidosis has been linked to an inborn error in fat metabolism. The observations that atherosclerosis and hypercholesterolemia frequently coexist,[1, 2] that both can be produced in animals following cholesterol feedings,[3] and that atherosclerosis is unusual when people eat little animal fat, favor this concept.[4–8] The unusual physical state and the abnormal ratio of certain circulating lipids that have been noted in patients with atherosclerosis,[9–12] as well as the increased cholesterol content of the actual vascular lesions[13–15] also support this view. However, in spite of these and other subtle correlations, an unequivocal relation has not been established between atherosclerosis in man and a disturbance in lipid metabolism.

In 1949 Thannhauser and Stanley reported a method for the study of the metabolism of neutral fat in human subjects utilizing I^{131}-labeled olive oil.[16] It had several distinct advantages: (1) the required amount of labeled fat was small and well tolerated, (2) the radioactive iodine was easily measured in the serum, (3) the proportion of the radioactive iodine that split off the fatty acid molecule could be determined and information could be gained as to the speed of catabolism of the labeled fat.

Since this initial effort, we[17] and others[18–22] have used this technic to study the absorption and utilization of fat in normal individuals and in patients with evidence of malabsorption.

The present investigation extends the inquiry into the relationship between fat metabolism and the pathogenesis of atherosclerosis in patients with severe coronary artery disease. It details their response to a test meal of I^{131}-triolein and compares it with the results observed in normal patients and in individuals having hypercholesterolemia but not overt coronary atherosclerosis.

Material and Methods

I^{131}-triolein is a clear, colorless, oily liquid, at room temperature. Repeated assays have shown that 98 to 100 per cent of the I^{131} is bound to neutral fat. The bond is stable in gastric juice, bile, pancreatic juice, and 25-per-cent hydrochloric acid.

The radioactive iodine circulating after the ingestion of the test meal consists of 2 fractions. The first is contained in the fat that is in transport as lipoprotein. Usually we have found that this portion does not exceed 50 per cent of the total radioactivity.

The second fraction is derived from the splitting of the iodine-fatty-acid bond during utilization. The concentration of this inorganic fraction depends upon the rate at which the fat is utilized and the speed of renal excretion. The influence of the thyroid on this fraction is negated by the use of blocking agents prior to the test meal.

The technic for this test has been described before[17] and is briefly as follows:

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TABLE 1.—*Results of Radioactive Fat Tolerance Test in Normal Subjects and Patients with Coronary Atherosclerosis and Hypercholesterolemia*

			Peak values (%)		24-hour values (%)	
			No CAD*	CAD	No CAD	CAD
Whole blood radioactivity	Normal chol.	Mean	11.7	13.6	2.1	4.3
		S.D.†	2.5	4.8	0.9	2.0
	Elevated chol.	Mean	17.0	16.6	5.9	5.3
		S.D.	5.2	5.2	3.4	2.2
Lipid blood radioactivity	Normal chol.	Mean	3.7	6.2	0.2	0.5
		S.D.	1.2	2.7	0.1	0.4
	Elevated chol.	Mean	8.3	9.2	1.8	0.8
		S.D.	3.3	4.1	1.7	0.6
Lipid/whole blood radioactivity	Normal chol.	Mean	33	48	11	13
		S.D.	8	12	5	9
	Elevated chol.	Mean	58	56	30	18
		S.D.	18	18	17	12

*CAD=Coronary artery disease
†S.D.=Standard deviation

After a 12-hour fast each patient was given a test meal containing 25 μc. of I^{131}-triolein in a total volume of 1 ml./Kg. of peanut oil. Venous blood samples were taken at 2-hour intervals until a maximum radioactivity level was reached, and then 24 hours after. A 2-ml. aliquot of unclotted blood was counted in a scintillation well counter (whole blood radioactivity). Another aliquot, treated with potassium iodide and trichloracetic acid to separate the lipoprotein-bound iodine, was also assayed for radioactivity. The total blood volume was assumed to be 7.2 per cent of the body weight. With the given activity in the 2-ml. portions and the calculated total blood volume, the total whole blood and lipid blood radioactivity were determined and expressed as a percentage of the initially ingested fat.

The total urine output was collected for 24 hours after the meal, and was also assayed. In some cases, stools were also collected over a 72-hour period.

A total of 50 patients was studied; they were divided into 4 groups: Group 1 consisted of 15 healthy men between the age of 20 and 35. Group 2 was comprised of 15 men who were less than 50 years of age and who suffered a previous myocardial infarction. The fasting cholesterol values in both of these groups were consistently less than 250 mg. per cent (range 130-250, mean value, 190 mg. per cent). Group 3 included 10 men qualified as in group 2 except that the mean cholesterol was increased beyond 275 mg. per cent (range 275-600, mean value 330 mg. per cent). Group 4 consisted of 10 men without overt coronary artery disease but with definite hypercholesterolemia (mean value 350 mg. per cent, range 290-650).

RESULTS

The results are presented in figures 1 to 5 and tables 1 and 2.

After ingestion of the labeled-fat test meal, the blood radioactivity increased to a peak value, and then gradually declined. In general, the maximum values for the whole-blood and lipid-blood activity occurred at the same time. This was within 6 hours in the normal subjects, but later than 6 hours in a large percentage of the others.

Statistical analysis of the data showed that the most valuable information was obtained by studying the whole-blood, lipid-blood, or lipid/whole-blood ratio at its peak level, but

TABLE 2.—*Number of Patients Showing Abnormal Results in Radioactive Fat Tolerance Test*

		Peak values			24 hour values	
Group	Total no.	Whole blood	Lipid blood	Lipid/whole blood radioactivity	Whole blood	No. showing more than 1 abnormality
1	15	1	1	0	1	0
2	15	5	12	7	8	12
3	10	6	8	7	7	6
4	10	8	9	6	7	8

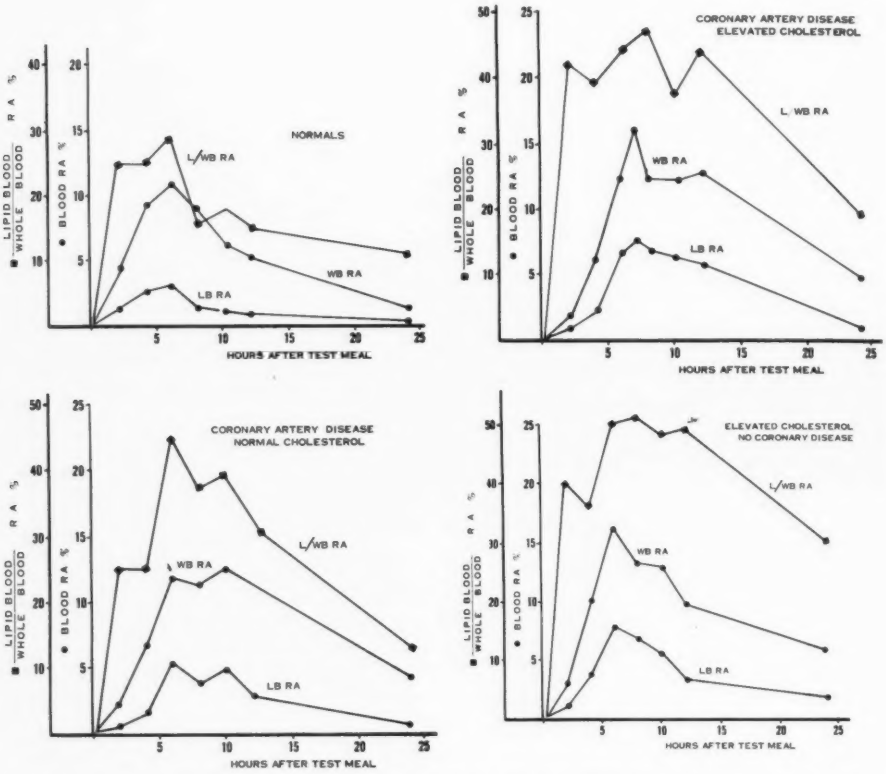

FIG. 1 *Top, left.* Mean values of whole blood (*WB*) and lipid blood (*LB*) radioactivity (*RA*), and lipid/whole blood ratio in normal controls.

FIG. 2 *Bottom, left.* Mean values of whole blood and lipid blood radioactivity, and lipid/whole blood ratio in patients with coronary atherosclerosis and normal cholesterol levels.

FIG. 3 *Top, right.* Mean values, whole blood and lipid blood radioactivity, and lipid/whole blood ratio in patients with coronary atherosclerosis and elevated cholesterol levels.

FIG. 4 *Bottom, right.* Mean values, whole blood and lipid blood radioactivity, and lipid/whole blood ratio in patients with hypercholesterolemia but no evidence of coronary artery disease.

only the total blood radioactivity at the 24-hour period.

At the peak time, significant differences existed between the normal subjects and the patients with coronary artery disease ($p = < .05$), as well as between the normal and hypercholesterolemic subjects ($p = < .001$). When coronary artery disease was present concomitantly with elevated cholesterol levels, these differences were exaggerated, especially in the case of the lipid-radioactivity values.

At the 24-hour interval, only whole-blood determinations showed significant differences ($p = < .001$) between cardiac and noncardiac, and normal and hypercholesterolemic subjects.

The values for the 24-hour lipid-radioactivity and the lipid/whole-blood ratios, showed variations difficult to evaluate because of the small magnitude of the counts involved, whereby minor changes could produce marked alterations in the ratios.

Possibly even more significant than a comparison of the mean values of the various groups studied was the recognition of the in-

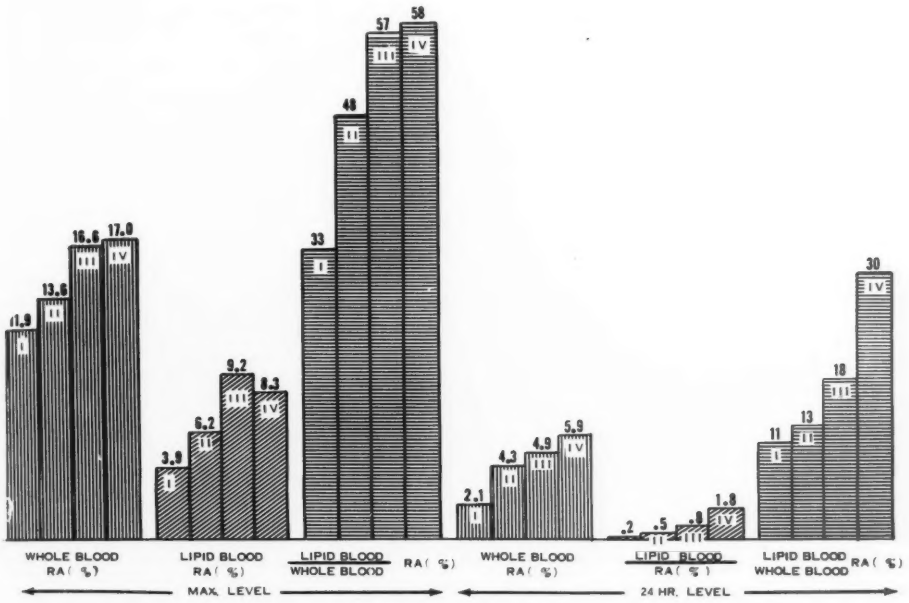
WHOLE BLOOD RA(%)
LIPID BLOOD RA(%)
LIPID BLOOD / WHOLE BLOOD RA(%)
MAX. LEVEL
WHOLE BLOOD RA(%)
LIPID BLOOD RA(%)
LIPID BLOOD / WHOLE BLOOD RA(%)
24 HR. LEVEL

FIG. 5. Mean values, whole blood and lipid blood radioactivity, and lipid/whole blood ratio at peak time and after 24 hours in groups of patients studied.

cidence of abnormal results within each individual group (table 2). If normal values were assumed to be equal to the mean plus 1 standard deviation, 80 per cent of the group 2 patients, 80 per cent of group 3 patients, and 90 per cent of group 4 demonstrated some abnormality in their curve. Three patients in the control group (20 per cent) also exhibited some abnormality.

DISCUSSION

In the present study attention has been directed to certain specific aspects of the blood radioactivity curve following the ingestion of isotopically labeled fat: (1) the maximum height of the total and lipid-bound radioactivity, (2) the time required for these levels to be reached, (3) the amount of radioactivity remaining after 24 hours, and (4) the lipid/whole-blood radioactivity ratio during the period of the test. Although these values are only a partial reflection of the complete metabolic cycle that follows a labeled-fat test meal, it is thought that they are the most informative, and upon them is based the substance of this report.

The responses in patients with coronary artery disease who had normal or elevated blood cholesterol values and in persons without obvious atherosclerosis with hypercholesterolemia, were singularly different from the controls. They were characterized by unusu-

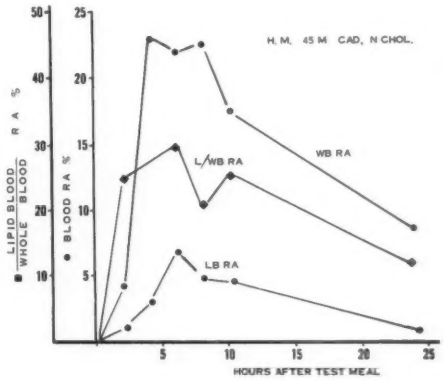

FIG. 6. Radioactive fat tolerance curves in patient with coronary atherosclerosis and normal cholesterol.

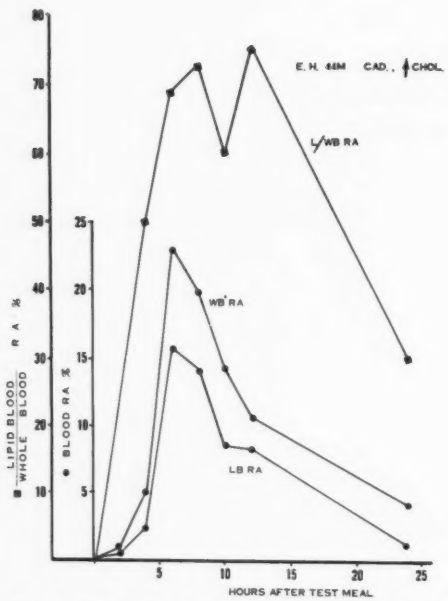

FIG. 7. Radioactive fat tolerance curves in patient with coronary artery disease and hypercholesterolemia.

ally high blood levels of total and lipid-bound radioactivity, delays in attaining these concentrations and abnormal 24-hour retention. In many, in addition, the lipid/whole-blood ratio showed that a major fraction of the radioactivity was present in the organic fraction. When coronary disease and elevated cholesterol levels were present at the same time, these abnormalities were exaggerated (figs. 6 to 8).

Any attempt to explain these absorptive patterns necessitates a knowledge of the various factors concerned.

Under normal conditions, at least 97 per cent of the radioactive fat is absorbed within 24 hours. However, the amount present in the blood at any specific interval is dependent on additional factors, notably the rate of utilization plus the pre-existing fat pool. When the ascending limb of the radioactive curve culminates in a higher-than-normal peak level, or continues its abnormal rise for more than 6 hours, an increased rate of absorption during this period of time may be responsible. This could stem from decreased intestinal motility which allows more time for the fat to be exposed to the absorbing surface, or a primary mucosal phenomenon may be responsible. Data showing that the intestinal mucosa is able to absorb abnormally high amounts of a basic foodstuff in certain conditions have already been advanced by Meyer and Yannoni.[23] They found that in certain mice with experimentally produced obesity an increased rate of glucose absorption may be present—an apparent compensatory mechanism for the hyperphagia.

On the other hand, abnormally high blood radioactivity levels may result from some abnormality in fat transport or an absolute or selective decrease in its catabolism. The delay in the disappearance of the isotope after 24 hours may be explained similarly.

Thus far the role of the pre-existing fat pool has not been taken into account. It may well be that in certain cases, e.g., those associated with hypercholesterolemia, the abnormal curves are a result of the hyperlipemia and its attendant chemical dilution. Further studies correlating the basal triglyceride and total fat values may help to clarify this problem.

The significance of the abnormalities in the curves of 3 of the control group cannot be assessed at this time. It is possible that these individuals are not "normal" but rather have asymptomatic coronary disease. Only a long-term follow-up of these and similar patients

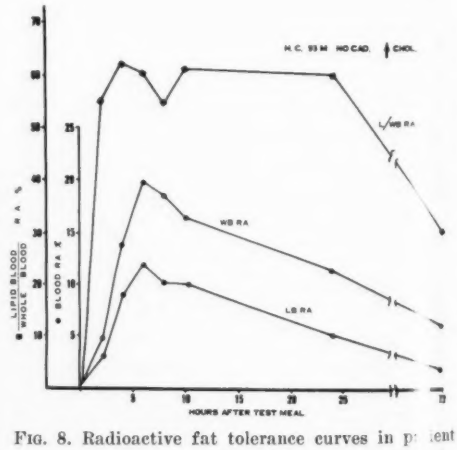

FIG. 8. Radioactive fat tolerance curves in patient with coronary artery disease and hypercholesterolemia.

will determine whether this measurement of impaired fat tolerance was an implication of latent disease.

The inability to define the precise mechanism responsible for the abnormal radioactive fat tolerance curves that have been obtained do not allow any major conclusions. It would nevertheless appear that this test offers an excellent means of studying fat metabolism. Whether correlations can be made between abnormal results and the presence of coronary atherosclerosis is a matter to be proved by further investigations.

Summary

1. Patients with coronary atherosclerosis and hypercholesterolemia exhibit characteristic blood radioactivity patterns following the ingestion of an I^{131}-triolein test meal.

2. These are exemplified by elevated whole-blood and lipid-blood radioactivity levels that persist even after 24 hours. When both coronary disease and elevated cholesterol levels are present, these abnormalities are exaggerated.

3. The radioactive fat tolerance test appears promising as a means of detecting the presence of derangements in lipid metabolism in asymptomatic individuals, and may also be used as a guide in evaluating treatment. The reversion of an abnormal curve to normal appears to be a more rational aim in any therapeutic approach to the problem of atherosclerosis, rather than the reduction of the blood cholesterol when it is elevated.

Acknowledgment

We acknowledge with thanks the cooperation and valuable assistance given to us by Dr. J. Gershon-Cohen, Director of the Department of Radiology of the Albert Einstein Medical Center, Northern Division, and also the technical help of our isotope technician, Miss Hettie Brenz.

Summario in Interlingua

1. Patientes con atherosclerosis coronari e hypercholesterolemia exhibi configurationes characteristic del radioactivitate del sanguine post le ingestion de repastos experimental con triolein a I^{131}.

2. Iste configurationes es typicamente representate per elevate nivellos (persistente mesmo post 24 horas) del radioactivitate de sanguine integre e de sanguine lipidic. In casos in que morbo coronari e elevate nivellos de cholesterol es presente, ambe iste anormalitates es exaggerate.

3. Le test del tolerantia de grassia radioactive es promittente como medio de detection del presentia de disrangiamentos del metabolismo lipidic in individuos asymptomatic. Illo es etiam usabile como guida in le evaluation del tractamento. Il pare que le reversion de un curva anormal a un forma normal es un objectivo plus rational de omne programma therapeutic in casos de atherosclerosis que le reduction de elevate nivellos de cholesterol in le sanguine.

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I do not find the heart in all creatures to be a distinct and separate part; for some, as you would say Plant-animals, have no heart; Colder creatures of a softer make, and of a kind of similarie constitution, such as are Palmer-worms and Snails, and very many things which are ingender'd of putrefaction and keep not a species, have no heart, as needing no impulsor to drive the nutriment into the extremities: For they have a body connate and of one piece, and indistinct without members; so that by the contraction and returning of their whole bodie, they take in, expell, move and remove the nourishment, being call'd Plant-animals; such as are Oysters, Mussles, Sponges, and all sorts of Zoophytes, have no heart; for instead thereof they use their whole body, and this whole creature is as a heart.—William Harvey. *De Motu Cordis*, 1628.

Studies of the Arterial Pulse Wave

ARTHUR W. FEINBERG, M.D. AND HENRY LAX, M.D.
With the technical assistance of William Urban

Previous studies have shown abnormalities of the arterial pulse wave in hypertensive subjects of all age groups. The major change has been diminution to disappearance of the dicrotic wave. The pharmacologic differences between epinephrine and norepinephrine offer a means of studying the mechanism of this change in the dicrotic wave. In the present study, normotensive subjects have had transient hypertension induced by the infusion of epinephrine and norepinephrine. The different effects of these drugs on their arterial pulse waves have been recorded.

IN A previous report,[1] describing observations on the arterial pulse wave in human subjects, a new technic was introduced for recording the pulse wave without intra-arterial puncture. The method has been shown to be sensitive and to give reproducible results. The accuracy of the recordings has been demonstrated by the similarity of simultaneous intra-arterial and extra-arterial tracings.

Figures 1 and 2 show typical instances of normal and abnormal arterial pulse waves as recorded by this technic. The major difference in the abnormal cases appears to be diminution to disappearance of the dicrotic wave. These changes in the dicrotic segment of the arterial pulse wave have been found in hypertensive subjects of all age groups as well as in patients with generalized arteriosclerosis, coronary arteriosclerosis, and diabetes mellitus.

The dicrotic wave has been ascribed to a reflected wave from the recoil of the blood column against the closed aortic valve. More recent studies[2-7] indicate that peripheral factors also play a role in the formation of the dicrotic wave. The technic described herein seemed to offer another means of studying the mechanism of the dicrotic wave.

The pharmacologic studies of Goldenberg and his group[8] have shown that although both epinephrine and norepinephrine produce comparable degrees of hypertension, they do so in different ways. The hypertensive action of epinephrine in man is due primarily to a large increase in cardiac output that overbalances a decrease in total peripheral resistance. On the other hand, hypertension induced by norepinephrine is produced in man by a striking increase in peripheral resistance with little or no change in the cardiac

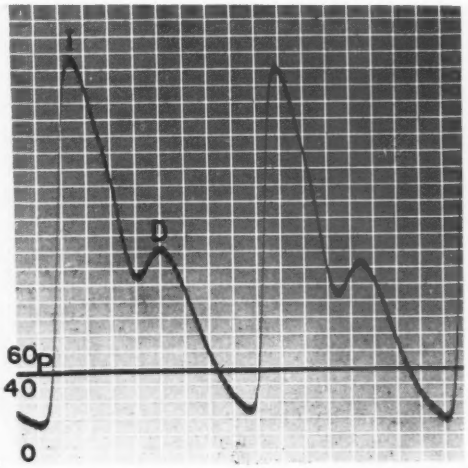

FIG. 1. Normal arterial pulse waves recorded from the third digit of a healthy 25 year old man. The *vertical lines* are time signals 0.1 second apart and the *horizontal lines* represent pressure increments of 10 mm. Hg in the cuff applied about the finger. The cuff pressure (*P*) is recorded simultaneously but independently of the components of the pulse wave. Note initial wave (*I*) and well defined dicrotic wave (*D*).

From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, Department of Hospitals, New York, N.Y., and the Department of Medicine, College of Physicians and Surgeons, Columbia University.

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output. It appeared that investigation of the effect of these 2 drugs, with their different central and peripheral actions, might help to explain the mode of origin of the dicrotic wave. Accordingly, the present study has been carried out on the effect of intravenous infusions of epinephrine and norepinephrine, in quantities sufficient to produce significant hypertension, on the dicrotic wave of presumably healthy, normotensive individuals.

Method and Technic

A sensitive rubber cuff with an inelastic backing is applied to the external surface of the limb or digit. The cuff consists of a thin rectangular membrane 1½ by 3 inches cemented at the edges to a backing piece of rubberized cloth. A 1/8 inch I.D. nipple attached at the center of the cloth is connected to a 3 foot length of 1/8 inch rubber tubing. This tubing serves the dual purpose of inflating the cuff and connecting it to the recording chamber of a differential pressure transducer. The cuff is attached by an inelastic strap to the extremity to be examined.

The differential pressure transducer consists of a circular beryllium copper diaphragm 0.006 inch thick and 1½ inches in diameter, separating 2 air chambers. Air pressure required to inflate the cuff is introduced to both chambers, causing no deflection of the diaphragm. Pressure disturbances originating at the cuff, however, are conducted to the recording chamber only. These disturbances cause the diaphragm to deflect according to their intensity and direction.

Deflections of the diaphragm are transmitted by mechanical linkage either to a Statham absolute pressure strain gage or to a piezo-electric crystal cartridge that generates electric energy according to the mechanical motion imposed upon it. The crystal unit (Astatic microphone cartridge D-104) has an output of –45 db. referred to 1 volt per micro bar. Output from the crystal is amplified with a class A balanced push-pull amplifier with continuous variable gain from 0 to 16 db. max. The amplifier feeds a dual-coil string-type mirror galvanometer.

Permanent recordings are made on 12 cm. wide electrocardiographic paper, with a Cambridge 3 speed camera. Camera speeds are 12½, 25, and 50 mm. per second. Timing marks appear as equally spaced vertical lines. Recordings can also be made intra-arterially and taken on direct-writing electrocardiograph paper.

The frequency response of the entire system from cuff to galvanometer shows the response to be substantially flat to 40 cps., which is well above the 5 to 6 cycle range encountered in studying arterial pulse waves.

Continuously variable gain control enables the operator to standardize the amplitude of recordings without affecting the configuration of the arterial pulse wave. This feature is of value in comparative studies over a period of time on the same subject. Recording at the same basic amplitude permits standardized conditions insofar as the instrument itself is concerned. The only variables then lie with the patient.

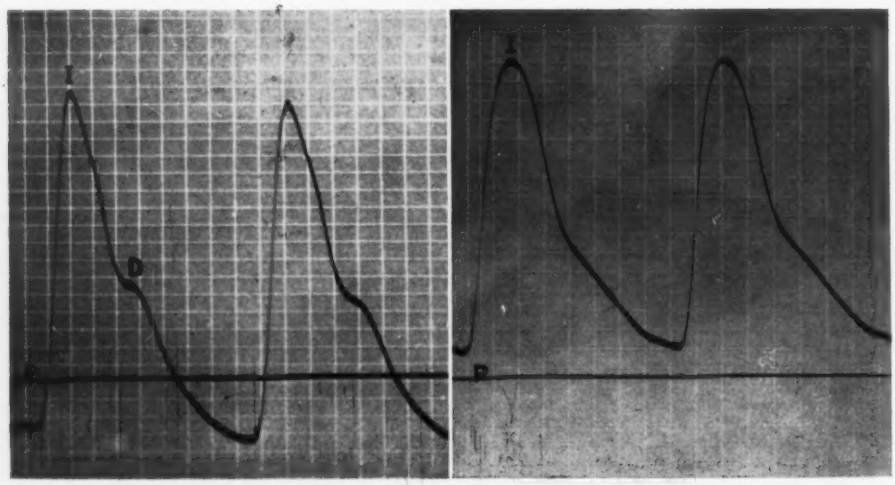

Fig. 2. *Left.* Abnormal arterial pulse wave. Note diminished size of dicrotic wave (*D*). The cuff pressure (*P*) is also recorded. *Right.* More severely abnormal arterial pulse wave showing a complete absence of the dicrotic wave.

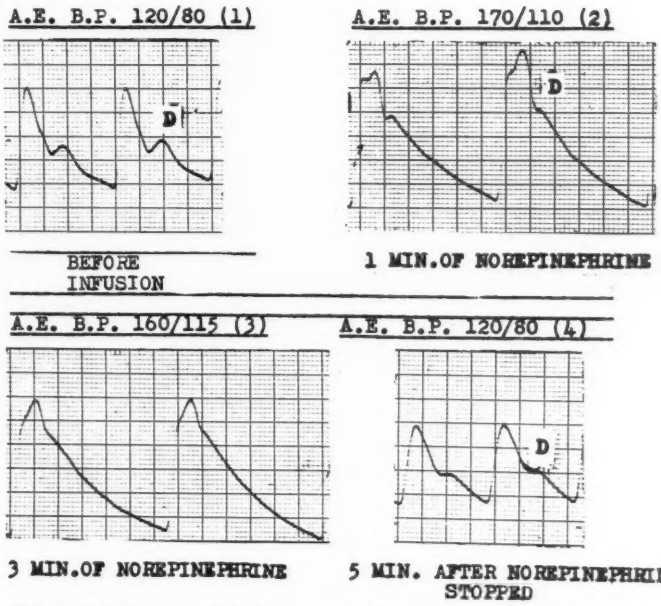

FIG. 3. Effect of intravenous infusion of norephinephrine on the arterial pulse wave of a 32 year old normotensive male subject. Note the diminution of the dicrotic wave (*D*) in *2* and its virtual disappearance in *3*. It starts to return in *4* after the blood pressure has returned to control levels.

All arterial pulse wave tracings during this study were recorded intra-arterially. A Cournand needle (18 gage, 2 3/64 inch. no. 488 LNR) was introduced into a brachial artery. Pulse pressure waves were transmitted to a Statham P-23A absolute pressure strain gage and a continuous intra-arterial pulse wave tracing was begun. After a control period lasting from 2 to 5 minutes, a previously introduced infusion of glucose and water was changed to an infusion containing either norepinephrine (Levophed) or epinephrine (Suprarenin, Winthrop). The blood pressure was taken by cuff at 1 minute intervals and in some cases was also recorded on the tracing. After 3 minutes of sustained elevation of systolic and diastolic pressures, the intravenous infusion was discontinued but the continuous intra-arterial pulse wave recording was maintained until the configuration of the pulse wave had about returned to its control appearance. This usually took 10 to 15 minutes. The blood pressure invariably fell to its baseline levels before the control pulse wave configuration was restored.

RESULTS

With Norepinephrine

Nine normotensive, presumably healthy subjects were given norepinephrine by intravenous infusion. In all individuals, as the blood pressure rose, the well defined dicrotic wave of the control intra-arterial pulse wave became smaller and finally disappeared completely. Upon discontinuing the norepinephrine, the dicrotic wave reappeared within minutes of the return of the blood pressure to control levels.

Figure 3 is illustrative of these changes. The subject was a 32 year old male hospital porter with no clinical evidences of vascular disease. His resting blood pressure was 120/80, and a well defined dicrotic wave is seen on his initial pulse tracing. The blood pressure rose to 170/110 after 1 minute of intravenous norepinephrine in doses of 0.4 μg. per Kg. per minute and the dicrotic wave became markedly smaller. The double peaking of the anacrotic wave has been seen in other subjects with hypertension, whether natural

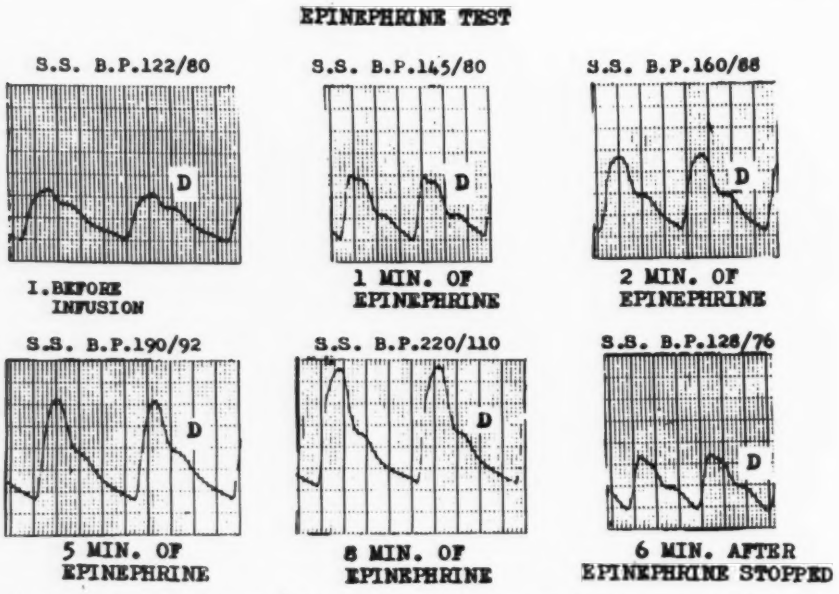

FIG. 4. Effect of intravenous infusion of epinephrine on arterial pulse wave. Although the amplitude of the entire wave increases with rise in blood pressure, dicrotic wave (*D*) is clearly seen at all times.

or induced. Its cause remains unexplained. After 3 minutes of sustained hypertension, the dicrotic wave completely disappeared. Five minutes after stopping the norepinephrine infusion, the blood pressure had returned to its control level of 120/80 and the dicrotic wave had started to become evident again. The study was discontinued in this patient before the dicrotic wave had recovered its full height.

With Epinephrine

Four normotensive, presumably healthy subjects were given epinephrine intravenously. Despite elevations of the systolic and diastolic blood pressure comparable to those seen in the experiments with norepinephrine, no basic change was noted in the configuration of the dicrotic wave. Specifically, the dicrotic wave was neither diminished nor had disappeared in any of the subjects studied, even though the over-all amplitude of the pulse wave increased as the blood pressure rose.

Figure 4 illustrates these changes in a 21 year old female hospital technician. Epinephrine was infused intravenously in doses of 0.4 μg. per Kg. per minute for a total of 8 minutes. During this time the blood pressure rose from 122/80 to a sustained peak of 220/110. Although the form of the arterial pulse wave reflected this change in the blood pressure, the dicrotic wave remained clearly defined in all tracings.

In one of the normotensive subjects (a 30 year old male technician) epinephrine and norepinephrine were given consecutively, with a 15 minute interval between the administration of the 2 drugs to permit return of the control pattern. The typical difference between the effects of epinephrine and norepinephrine are demonstrated in this case (fig. 5). Both drugs produced approximately the same elevation of blood pressure. Norepinephrine caused a complete disappearance of the dicrotic wave, whereas the dicrotic wave was undisturbed after the administration of epinephrine.

DISCUSSION

The mode of origin and propagation of the dicrotic wave has been investigated for years but remains incompletely understood. The

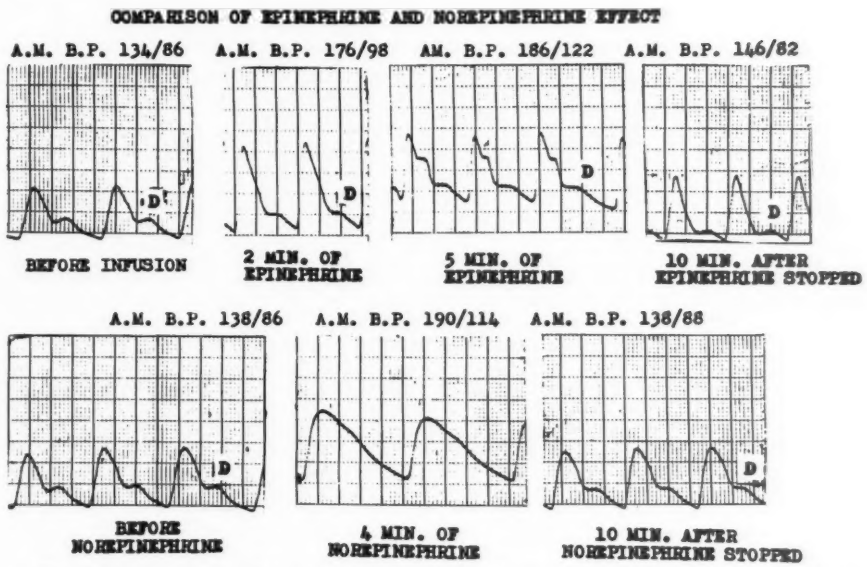

FIG. 5. Effect of epinephrine and norepinephrine given consecutively to the same patient after a 15 minute interval. Note persistence of the dicrotic wave (*D*) in the epinephrine tracings and its disappearance after norepinephrine. Both drugs gave comparable elevations of blood pressure.

classic theory explains the dicrotic peak as a reflected wave initiated by the recoil of the arterial blood column against the closed aortic valve. The studies of Hamilton, Remington, and Dow,[2-5] Wiggers,[6] and Alexander[7] have shown that the arterial pulse wave is progressively transformed in its passage down the aorta and its arterial branches, suggesting that the physiologic state of the peripheral vessels may play an important part in influencing the appearance of the dicrotic wave. Our initial studies[1] also suggested that changes in the peripheral arteries determine the presence or absence of the dicrotic wave of the arterial pulse. It was found, for example, that the dicrotic wave was markedly abnormal in hypertensive subjects of all age groups, in patients with peripheral arteriosclerosis, and in diabetic patients as young as 1[illegible] years of age.

The results of the present study would seem to support this view. In the 4 subjects given epinephrine, the dicrotic wave was not basically altered although the blood pressure rose significantly. On the other hand, in all 9 patients who received norepinephrine, the dicrotic wave was abolished or markedly reduced in size, despite a similar rise in blood pressure. These findings are well explained by what is known of the pharmacologic differences between the 2 drugs. Goldenberg and others[8] have shown that the actions of epinephrine and norepinephrine in man are similar only in that they both produce significant elevations of blood pressure. The hypertensive effect of norepinephrine is due to an increase of total peripheral resistance, with no significant change in cardiac output. Epinephrine, on the other hand, raises the blood pressure predominantly by a central action on the heart, increasing the rate and force of cardiac contractions and the cardiac output. The peripheral resistance actually decreases, because of an over-all vasodilating action.

The marked difference between the effects of epinephrine and norepinephrine on the dicrotic wave thus support the hypothesis that changes in the tonus of the arterial wall have significant effects on the configuration of the distinctive waves seen in arterial pulse tracings.

Summary

Previous studies have shown a diminution to disappearance of the dicrotic wave in the presence of clinical evidences of arteriosclerosis, diabetes mellitus, and hypertensive vascular disease.

Transitory hypertension was induced in 13 normotensive subjects by intravenous infusions of either norepinephrine or epinephrine. A continuous intra-arterial pulse-wave tracing was recorded from the brachial artery before, during, and after the infusions in most instances.

The pulse waves of all 9 subjects given norepinephrine demonstrated disappearance of the dicrotic wave as the blood pressure rose. The dicrotic wave reappeared as the blood pressure returned to normal. Contrariwise, 4 subjects given epinephrine had no change in the dicrotic wave despite comparable elevation of the blood pressure.

The different effects on the dicrotic wave may be related to the pharmacologic differences between the 2 drugs. Epinephrine hypertension is produced by an increased cardiac output in spite of a reduced total peripheral resistance; norepinephrine hypertension is caused by an increased peripheral resistance with little or no change in cardiac output.

The evidence presented lends support to the theory that peripheral factors play an important role in the production of the dicrotic peak of the arterial pulse wave.

Summario in Interlingua

Previe studios ha monstrate un diminution o dispariton del unda dicrotic in le presentia de manifestationes clinic de arteriosclerosis, diabete mellite, e hypertensive morbo vascular.

Hypertension transitori esseva inducite in 13 subjectos normotensive per infusiones intravenose de norepinephrina o de epinephrina. Un registration continue del unda del pulso intra-arterial esseva effectuate pro le arteria brachial ante, durante, e post le infusiones (in le majoritate del casos).

Le undas de pulso del 9 subjectos recipiente norepinephrina exhibiva disparition del unda dicrotic in association con le augmento d l pression de sanguine. Le unda dicrotic r - appareva quando le pression de sanguine r - tornava a nivellos normal. Del altere later , 4 subjectos recipiente epinephrina exhibi a nulle alteration del unda dicrotic in despec o de comparabile augmentos del pression de sa - guine.

Le differentia inter le effectos exercite sup r le undas dicrotic es possibilemente relationa e al differentias pharmacologic inter le duo dr - gas. Hypertension a epinephrina es produci e per un augmento del rendimento cardiac n despecto de un reducite total resistent a peripheric. Hypertension a norepinephri a es causate per un augmento del resistent a peripheric con pauc o nulle alteration del rendimento cardiac.

Le datos presentate supporta le theoria que factores peripheric ha un rolo importante in le production del culmine dicrotic que charac- terisa le unda del pulso arterial.

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Observations on Aberrant Renal Arteries Curving Around and Compressing the Renal Vein

Possible Relationship to Orthostatic Proteinuria and to Orthostatic Hypertension

By HILEL NATHAN, M.D.*

Some conditions, considered idiopathic or of only partially known etiology, may have an anatomic basis. Among such conditions are possibly certain postural or orthostatic syndromes related to the kidney such as orthostatic proteinuria and orthostatic hypertension. In the present work some anatomic observations on the renal pedicle are presented that seem to give support to this concept.

DETAILED descriptions of frequent and multiform variations of the vascular elements of the renal pedicle are to be found in the literature.[1-9] The subject has recently been well reviewed by Merklin and Michaels.[10] Embryologic interpretations of such variations have been given by Broman,[11] Jeidel,[12] Felix,[13] and Bremer.[14]

It is the purpose of the present work to describe a type of aberrant renal artery, curving around the renal vein, which by its particular course may have some importance in the causation of certain pathologic conditions. The only reference found in the literature to an artery having such a course is that of Rupert,[5] who recorded its presence in 2 out of 50 dissected bodies.

MATERIAL

The present report is based on the dissection of 400 renal pedicles in 200 dissecting-room cadavers.†

OBSERVATIONS

In 7 cases (3.5 per cent) an aberrant inferior polar renal artery, curving around the renal vein, was present in addition to the normal renal artery. Six of these were on the left side and 1 on the right. The vessel originated from the aorta (figs. 1 and 2) below the level of the corresponding renal vein, and proceeded upward and laterally behind the vein. At the upper border of the vein, the artery curved downward and descended in front of the vein, to reach the kidney near its lower pole. The artery thus described an arch over the renal vein. In all the left-sided cases the arch was lateral to the entrance of the suprarenal and testicular (or ovarian) veins into the renal veins. In 3 of these left-sided cases a testicular artery took origin from the aberrant arched renal artery.

In the single right-sided case the artery first passed posterior to the vena cava.

In all instances the artery was intimately related to the renal vein, which appeared constricted and angulated under the arch of the artery.

No cases were observed of superior polar arteries' having a similar course.

DISCUSSION

It is likely that an artery with the course just described is in a position to exert pressure on the renal vein, particularly in the erect posture. The deformations, constriction, and angulation of the renal vein appear to be the result of compression of the arch of the aberrant renal artery. The possibility also exists that the aberrant artery itself is compressed by the renal vein to some extent.

Instances of arteries acting as pathologic agents by compression have been described in various conditions. Thus aberrant renal arteries compressing the ureter have been considered to be etiologic agents in the production of hydronephrosis.[7, 8, 15-21]

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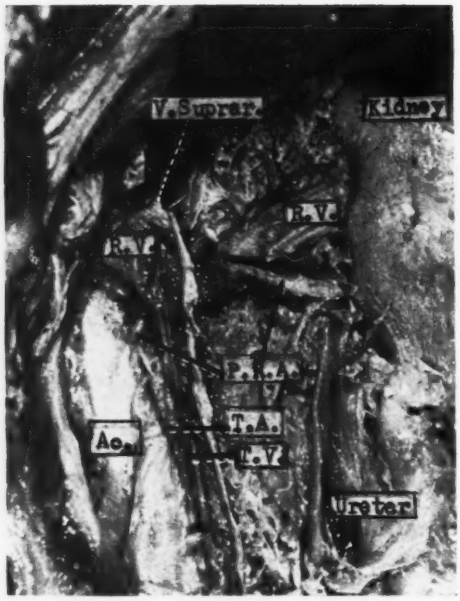

FIG. 1. Early stage of the dissection of the renal pedicle. Exposure of the kidney, the renal vein, and the inferior polar renal artery. The kidney and vascular elements have not been disturbed and are shown in their original position and relations. The polar renal artery is seen arching around the renal vein; the latter appears angulated and compressed under the arch. R.V., renal vein; R.A., normal renal artery; P.R.A., polar renal artery; Ao., aorta; V. Suprar., suprarenal vein.

Testicular or ovarian arteries, compressing the renal vein and acting as possible agents in the production of varicocele and orthostatic proteinuria, have been described by the author.[22, 23] In these cases the gonadal arteries followed an arched course around the renal vein, very similar to that of the renal artery here described. The fact that so frequently in the present study (in 3 cases out of 6 of the left side) a testicular artery took origin from the arched renal artery may point to a common embryologic origin of the 2 arteries.[11, 13, 14, 23]

A case in which an aberrant renal artery simultaneously produced hydronephrosis and varicocele, by compressing the testicular vein and the ureter, has been described by Campbell.[24]

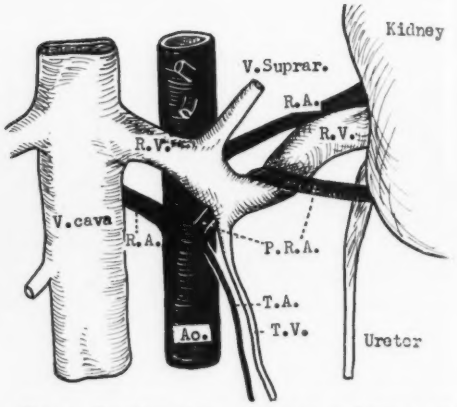

FIG. 2. Drawing of the same case as figure 1 after completion of the dissection. For key to abbreviations see figure 1.

A probable consequence of the compression of the renal vein by the aberrant renal artery described in the present study is the appearance of orthostatic proteinuria. It is generally accepted that increased venous pressure in the renal circulation is the cause of this condition. Among the etiologic factors considered as producing this increased venous pressure are compression of the vena cava by the liver (Bull[25]), and compression of the left renal vein by the "aortic-superior mesenteric arterial pincers"[26-31] by the arched testicular artery,[22, 23] or by the ligament of Treitz.[32]

If the aberrant renal artery here described is capable of compressing the renal vein, it is likely that the pressure in the vein would rise only in cases in which no collateral veins are present to drain the blood adequately from the renal vein. The presence of such collateral veins connecting the renal vein with the parietal lumbar veins spinal venous plexuses, and azygos systems was described by Lejars[33] and later by Faragasanu,[32] Anson et al.,[34, 35] and others. They are absent in a variable percentage of cases.

Since the arched renal artery passed laterally to the entrance of the testicular or ovarian veins, no interference in the normal circulation of these veins could be expected; no cases of varicocele or dilatation, such as were described for the arched testicular arteries,[22, 23] were recorded. Should a case

cur in which the arch passes medially, then the development of varicocele may be expected.

The possibility of some degree of compression of the renal artery by the renal vein has been mentioned. Were this the case, a kind of "postural, intermittent Goldblatt[36] mechanism" would be established. This might offer an explanation for some cases of orthostatic or postural hypertension described in medical literature. McCann and Romansky[37] have described cases of orthostatic hypertension and attributed the causes to the effect of nephroptosis on the renal blood flow. If both nephroptosis and the arching of the renal artery around the renal vein should occur together, the possibility of twisting and compression of the renal artery would be greater and the probability of causing orthostatic hypertension would be increased.

Ruppert,[5] in describing the 2 cases of renal arteries arching around the renal veins mentioned previously, discussed the possibility of such arteries', when combined with atypical floating kidneys, producing the symptoms of Dietl's crisis. He attributed these crises to twisting of the nervous plexuses surrounding the renal artery.

The importance of these variations of the vascular elements of the renal pedicle in surgery of this region as well as in the interpretation of renal angiograms requires no emphasis. The terminal character and segmental distribution[3, 26, 38] of the polar renal arteries has to be borne in mind in any surgical intervention.

Summary

An aberrant inferior polar renal artery of aortic origin, arching around the renal vein, is described. This was found in 7 cases (3.5 per cent) of 200 cadavers (400 renal pedicles dissected). Six cases were located on the left side and 1 on the right.

This kind of artery could be the cause of compression of the renal vein, particularly in the erect posture. The possible consequences of such compression are discussed with special reference to orthostatic proteinuria.

The possibility is considered of the aberrant artery described being partially compressed by the renal vein, again particularly in the erect posture. Should this occur, an "intermittent Goldblatt mechanism" might be established that would offer an explanation of the etiology of some cases of orthostatic hypertension.

Acknowledgment

I am deeply indebted to Professor J. L. Angel, of the Daniel Bough Institute of Anatomy of the Jefferson Medical College, and to Professor R. G. Williams, of the Department of Anatomy of the Pennsylvania University Medical School, for making the material of their respective departments available to me for study. I am also grateful to the personnel of these departments for their technical help. To Dr. G. Gitlin I express my gratitude for his assistance in the revision of the manuscript, and to Mrs. E. Salomon for the photographs and execution of the drawing.

Summario in Interlingua

Es describite un typo de aberrante arteria renal infero-polar de origine aortic que forma un arco circa le vena renal. Illo esseva trovate in 7 ex 200 cadaveres (3,5 pro cento) in le curso del dissection de omne le 400 pediculos renal. Sex del casos esseva trovate al latere sinistre, le septime al latere dextere.

Iste typo de arteria pare capace de causar le compression del vena renal, specialmente in postura erecte. Le consequentias possibile de un tal compression es discutite con referentias special a proteinuria orthostatic.

Es etiam considerate le possibilitate que le arteria aberrante del typo hic describite es comprimite illo mesme per le vena renal, de novo specialmente in postura erecte. Si isto occurre, il resultarea le establimento de un "intermittente mechanismo de Goldblatt" forniente un explication del etiologia de certe casos de hypertension orthostatic.

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Pulse Characteristics of Abdominal Aortic Aneurysm and of the Femoral Artery Distal to It

By EMBREE H. BLACKARD, M.D.

The advent of successful surgical treatment of abdominal aneurysm has increased the importance of detection and diagnosis of these lesions. The author has studied the pulse characteristics of abdominal aortic aneurysm and the distal femoral artery, and reports his results.

ANEURYSM of the abdominal aorta is of current interest because of its apparent increasing incidence, now occurring in at least 1.5 per cent of autopsies[1] and its successful surgical management, which according to Wright[2] was first reported by Dubost in 1951. The diagnosis depends on the presence of abdominal or back pain, on palpation of a pulsatile abdominal mass with or without tenderness, with or without a bruit, on x-ray evidence of a soft-tissue mass or calcification in the wall of the aneurysm, or, finally, on aortography. The width of the aneurysm as determined by palpation or x-ray is of prognostic significance, since only 4 to 18 per cent of aneurysms under 6 to 7 cm. in width found at autopsy have ruptured, as compared to 72 to 82 per cent of those over 6 to 7 cm.[3, 4] At present, the diagnosis of small aortic aneurysms is unsatisfactory, especially in obese patients.

There have been many references in the older literature to the effect of an aneurysm on the pulse distal to it. A decreased pulsation below the aneurysm was first described by William Harvey in 1628. According to Marey,[5] this was also noted by Hodgeson and Broca, and by 1883 was a well accepted observation. Whittlesey[6] refers to series by Hare and Holder, and Boyd and Kampmeir in which this finding was noted, and stated that it was a general postulate that aortic aneurysms reduce the amplitude of propagated pulses. Valleix, Weber, and Marey,[5] in addition, believed that an aneurysm produced a delay in the presentation of the distal pulse. Marey[5] constructed an artificial system whereby he transmitted a pulsation through a channel containing an aneurysmal pouch and recorded a pulsation of less amplitude and delayed peak force than when the same pulsation was transmitted through a serial channel of normal size. He compared these tracings with those of patients with subclavian aneurysms, which showed the same decreased amplitude and delayed peak in the radial pulse on the side below the aneurysm. He concluded that an aortic aneurysm would have these same qualitative changes, though to a lesser degree, because of its smaller size in relation to the size of the vessel. Whittlesey found[6] in constructing an artificial saccular aneurysm of the aorta that a volume of 400 ml., which doubled the capacity of the system, was required to decrease the peripheral pulse below the central pulse. Wright,[2] referring specifically to pulses below abdominal aortic aneurysm, found a diminished or absent pulsation below the aneurysm in 11 per cent. Marey also recorded the pulsation of the aneurysm itself, although it was necessary to record from the side of the aneurysm in order to attenuate the amplitude. He found the tracing resembled that of the carotid. Stokes[7] believed that the timing of the aortic pulsation was of diagnostic significance in differentiating aortic aneurysms from abdominal

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pulsations in hysterical women and from some transmitted pulsations. There are no data on the transmission of the pulse wave in aortic aneurysms.

The purpose of the present study is to record pulsations over aortic aneurysms and femoral arteries distal to them and to determine if there are any alterations from normal in amplitude, form, or transmission time.

Subjects and Methods

Twelve patients were studied. Their abdominal aneurysms varied in size from 3 to 10 cm. in width, with 10 of the 12 less than 7 cm. Only 4 had symptoms referable to an aneurysm; 8 had abdominal pulsations; 2 had aneurysms found accidentally by x-ray for nonrelated conditions, and 2 had aneurysms found at operation for nonrelated conditions. Three of the aneurysms were saccular, 1 of these in association with a diffuse aneurysm. Seven young and 5 normal subjects between the ages of 50 and 70 were studied as controls.

Recording of the pulsations of the aneurysms and of the femoral arteries were made with a bellows pickup mounted on a crossbar, transformed by a piezoelectric transducer, and recorded on a 4-channel Sanborn 150 recorder. The apparatus was as described by Eddleman et al.[8] for recording precordial movements.

Multiple tracings were taken along the course of the aorta, but no advantages were found over that of recording from a single point at the maximum pulsation as palpated. The tip of the pickup was pushed to the point of damping and then released until the maximum pulsation was obtained. The string settings were maintained constant, and the results were reproducible in the same patient on different days. In several obese patients it was necessary to have the abdomen depressed on each side of the pick-up by an assistant. The higher of the 2 femoral pulsations was used in the calculation.

The amplitude of aortic and femoral pulsations was measured as millimeter displacement on graph paper, with no determination of the actual displacement of the pick-up. The femoral/aortic ratio was calculated; the times were measured from the onset of the QRS of the electrocardiogram to the upstroke of the carotid, aortic, and femoral pulsations; the carotid and aortic pulsations were studied as to anacrotic time, "systolic time" (the time from onset of the upstroke to the incisura), and their ratio, and the level of the incisura above the end-diastolic level. The femoral pulsation was studied as to build-up time and "systolic time." These were calculated as described by Kroeker and Wood.[9]

Results

The range of amplitude of the aneurysm was 80 to 1,200 mm., that of the normal cases was 3 to 370 mm., with 5 cases of aneurysm and 5 normal cases falling in the 80 to 370 mm. overlap range.

Femoral pulsations distal to the aneurysm averaged 170 mm. (range of 50 to 370 mm.) as compared to the averages in older normal subjects of 145 mm. (range of 28 to 280 mm.) and in young normal subjects of 166 mm. (range of 30 to 260 mm.).

The ratio of femoral to aortic pulsations was more than 1.0 in all the older normal subjects, in 5 of 7 young normal subjects, and in only 1 of 9 patients with aneurysms. Of the 7 patients with aneurysms but without clinical peripheral vascular disease, 5 had femoral/aortic ratios between 21 and 26 per cent.

The onset of QRS to carotid upstroke averaged 0.13 second with a range of 0.10 to 0.15 in the patients with aortic aneurysms, 0.12 with a range of 0.10 to 0.15 in the older normal subjects, and 0.13 with a range of 0.11 to 0.14 in the younger normal subjects. The onset of QRS to the abdominal aortic upstroke was 0.16 with a range of 0.11 to 0.18 in the patients with aneurysms, 0.16 with a range of 0.13 to 0.19 in the older normal subjects, and 0.18 with a range of 0.17 to 0.20 in the younger normal subjects. The onset of QRS to the femoral upstroke was 0.17 with a range of 0.13 to 0.20 in the patients with aneurysms, 0.18 with a range of 0.14 to 0.21 in the older normal subjects, and 0.21 with a range of 0.18 to 0.22 in the younger normal subjects. The time from the carotid upstroke to the femoral upstroke averaged 0.04 second in the patients with aneurysms, 0.06 in the older normal subjects, and 0.08 in the younger normal subjects. The transmission time from onset to femoral pulsation to onset of dorsalis pedis pulsation in 1 older normal person was 0.06 second, and in 1 young normal subject was 0.13 second.

The aortic pulsation resembled the carotid in configuration and had the same characte

ties. The anacrotic time was 0.04 to 0.07 second; the systolic time in patients with aneurysm averaged 0.25 with a range of 0.22 to 0.29; in older normal subjects it was 0.25 with a range of 0.21 to 0.28 and in younger normal subjects was 0.28 with a range of 0.25 to 0.32. There was no variation in the anacrotic time or systolic time between the abdominal aortic and carotid pulsations in any given patient. The ratio of anacrotic time to systolic time varied from 14 to 27 per cent in patients in all groups. The build-up time and systolic time in the femoral arteries were the same for patients with aneurysms as for the normal subjects. The height of the incisura from end-diastolic level varied from 40 to 80 per cent of the total amplitude in the carotid, and 25 to 60 per cent in the abdominal aorta.

There were no differences in any respect between the 3 patients with saccular aneurysms and those with diffuse aneurysms of the aorta.

Discussion

This study failed to demonstrate any consistent effect of an aortic aneurysm on the pulsation below the aneurysm in amplitude, form, or transmission time of the pulsation. Because of the wide range in amplitude of the femoral pulsations, however, it cannot be proved that in any given patient the amplitude was not decreased from what it would have been if the aneurysm had not been present. There were no characteristics of the aortic pulsation, either in location, contour, or otherwise, that would be of diagnostic value. The amplitude of the pulsation was greater than in the normal subjects and showed a rough correlation with the size of the aneurysm, but there was a significant degree of overlapping of the normal and aneurysm groups. No pressure measurements were taken inside the aneurysm, and it cannot be determined if the increased amplitude reflected an actual increase in lateral pressure due to decreased velocity and subsequent increase in pressure in accordance with Poiseuille's law, or if the intravascular pressure were normal but produced a greater displacement due to increased distensibility of the vessel wall, or by acting over a larger surface area. It is of interest that 5 of 7 patients with aneurysms had a femoral/aortic ratio of 21 to 26 per cent. A larger number of patients is necessary to determine whether or not this is a significant correlation.

The figures for transmission time from onset to QRS to onset of femoral pulsation correspond to those found in young normal subjects by Schnabel et al.[10] (0.205 second), The values for the older groups were 0.17 and 0.18 second, which are consistent with the increased pulse wave velocity known to occur with age. The systolic time was found to be shorter than the 0.275 to 0.306 or the 0.296 to 0.321 range obtained by Lombard and Cope[11] and Kroeker and Wood,[9] respectively. There was a difference in systolic time between the young normal subjects and both older groups, with a shorter systolic time not related to heart rate in the older groups.

Summary

Pulsations were recorded over 12 abdominal aortic aneurysms and over the femoral arteries distal to the aneurysms. The tracings were analyzed and compared to the carotid pulsation of the same subject and the pulses of normal old and young subjects.

The amplitude of the abdominal pulsation was increased in the patients with aneurysms but there was a significant degree of overlapping with the normal subjects.

The femoral/aortic ratio was almost always greater than 1.0 in the normal subjects, was less than 1.0 in patients with aneurysms, and in 5 of 7 instances the femoral pulse was one fourth to one fifth of the aortic pulse.

There was no demonstrable effect of the aneurysm on the femoral pulsation below, either in respect to amplitude, contour, or velocity of transmission of the pulse wave.

Pulsations of saccular aneurysms showed no significant differences from those of diffuse aneurysms.

These studies have revealed no demonstrable

advantage of recording abdominal and femoral pulsations in cases of suspected aneurysm, as compared with manual palpation and appropriate x-ray studies.

Summario in Interlingua

Le pulsationes esseva registrate supra 12 aneurysmos del aorta abdominal e supra le arterias femoral a sitos distal con respecto al aneurysmos. Le registrationes esseva analysate e comparate con le pulsation carotidic del mesme individuos e con le pulsation de normal subjectos de etates juvene e avantiate.

Le amplitude del pulsation abdominal esseva augmentate in le patientes con aneurysmos sed il existeva un area significative de coincidentia del scala de valores in iste patientes con le scala del valores in subjectos normal.

Le proportion femoral/aortic esseva quasi semper supra 1,0 in le subjectos normal. Illo esseva infra 1,0 in le patientes con aneurysmos, e in 5 ex 7 casos le pulso femoral esseva inter un quarto e un quinto del pulso aortic.

Esseva constatate nulle effecto demonstrabile del aneurysmo super le pulsation femoral plus in basso, e isto valeva con respecto al amplitude, al contorno, e al velocitate transmissional del unda del pulso.

Le pulsation de aneurysmos saccular non exhibiva ulle differentia significative in comparation con le pulsation de aneurysmos diffuse.

Iste studios ha revelate nulle demonstrabile avantage de registrar pulsationes abdominal e femoral in casos de suspicion de aneurysmo, comparate con le methodo de palpation manual e del appropriate studios roentgenologic.

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The Determination of Cardiac Output by the Dilution Method without Arterial Sampling

I. Analytical Concepts

By William J. MacIntyre, Ph.D., Walter H. Pritchard, M.D., and Thomas W. Moir, M.D.

The selection of an external site for a radioisotope determination of cardiac output is discussed with respect to satisfying the analytical conditions of the Stewart-Hamilton dilution equation. Examples of both single-chamber and multichamber recording are illustrated, along with a discussion of the difficulties of curve calibration and extrapolation from multiple sites. The development of a method independent of critical placement or patient variability is described.

ALTHOUGH earlier determinations of cardiac output in this laboratory[1-3] by the radioisotope dilution method were performed by isolating the flow from a specific artery, such sampling is not required by the general formulation of the method. Since the obviation of the arterial puncture would considerably simplify this measurement clinically, studies have been extended[4-9] to determine cardiac output by focusing a gamma ray detector externally over the region of the cardiac chambers or great vessels. We have been concerned since 1951 with the selection of a site that could be observed externally with sufficient reliability for this technic to be accepted as a routine clinical measurement. Many sites of arterial flow may be chosen for quantitation of a dilution curve of cardiac output; therefore, the problem has resolved to a selection of such sites and technics that will not be critically affected by variations in patients.

It is the object of the following investigation to examine the choice of the external site with respect to satisfying the conditions of the Stewart-Hamilton[10, 11] dilution equation. This study has included the relationship of the recorded curve of the counting rate to dilution quantities, the calibration of in vivo recording, and the problems of adequate extrapolation of the dilution curve.

Method and Calculation of Cardiac Output

The determination of cardiac output by the dilution method is based on the measurement of the varying concentration of the injected material as it passes through the heart. If a small volume of highly concentrated material is injected into the inflow tract, the average dilution of the material coming out of the heart will be a direct indication of the volume passing through the heart and causing this dilution. The measurement of the change of concentration during a definite interval thus permits the output to be expressed as volume of flow per unit time. The dilution curves obtained in the following investigation have been measured by the recording equipment described previously.[1-3] Iodinated human serum (I^{131}) albumin was used as the injected material, and an external scintillation counter was focused at the site of interest. The selection of collimation has been a function of the site chosen and will be discussed, in reference to the anatomic placement, in an accompanying paper.[12]

Since the same total injected material, I, must come out of the heart as was injected into the inflow tract, this quantity of injected material must be equal to the product of the flow rate, F, multiplied by the concentration of the tagged material, c, in the blood, integrated over the entire

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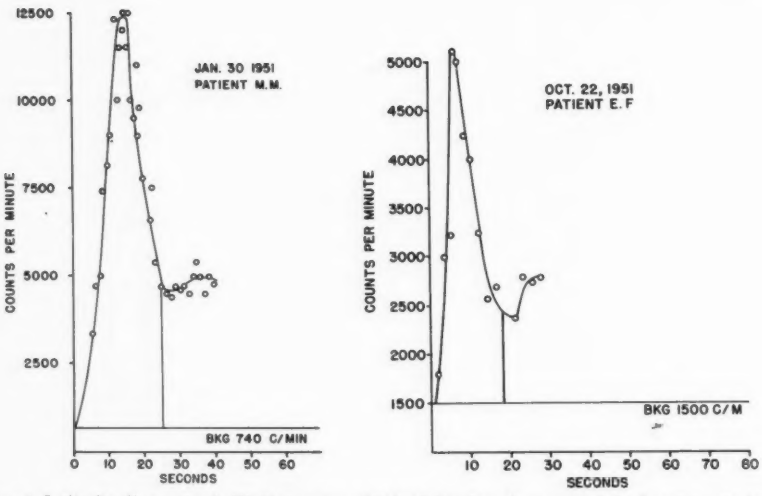


FIG. 1 *Left.* Cardiac output dilution curve obtained by focusing over right heart posteriorly. Collimator of 1.3 cm. aperture and 10.5 cm. length was used. Calculated cardiac output 7.1 L./min. BKG = background in counts per minute.

FIG. 2 *Right.* Cardiac output dilution curve obtained by posterior focusing on aortic arch following fluoroscopic localization. Calculated cardiac output 6.1 L./min.

time of the primary circulation. This is represented by the equation

$$I = \int_0^\infty Fcdt \qquad (1)$$

and if F, the flow rate or cardiac output, is constant during the time of measurement

$$F = \frac{I}{\int_0^\infty cdt} \text{ or } F = \frac{I}{A} \qquad (2)$$

where A represents the integral of the primary dilution curve $\int_0^\infty cdt$

The calculation of the cardiac output by the dilution method is then dependent only on the recording and integration of the dilution curve with time. This recording, which is uncomplicated for an externally isolated peripheral artery or direct arterial sampling, does present additional problems when extended to viewing the concentration of radioactive material in the large central vessels or chambers.

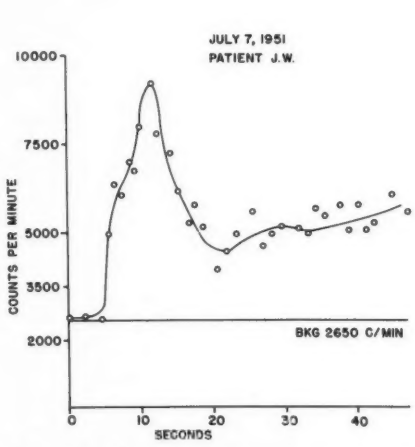
Relation of Counting Rate to Dilution

The first problem involves the relationship of the concentration curve, as recorded in counts per minute, to a dilution of the injected radioactive material in terms of microcuries per milliliter. In the following investigation, this relationship was obtained by assaying a sample of venous blood in vitro and equating this blood concentration in microcuries per milliliter to the response in counts per minute of the detector to this same concentration in vivo at the selected site.

Even in measurements involving arterial puncture, calibration of the counting system has been accomplished by withdrawing a blood sample at a time sufficiently long after injection for the concentration to be considered as constant over the period of its measurement. The final concentration in microcuries per milliliter is then determined in vitro. The injected dose, I, is equal to the product of the concentration c_f, and the equivalent volume of dilution, V. Equation 1 is thus reduced to

$$F = \frac{c_f \cdot V_d}{A} \qquad (3)$$

It should be emphasized that V_d is not necessarily the circulating blood volume usually calculated by dilution methods, but actually the volume of dilution of the injected material at the time when the sample was



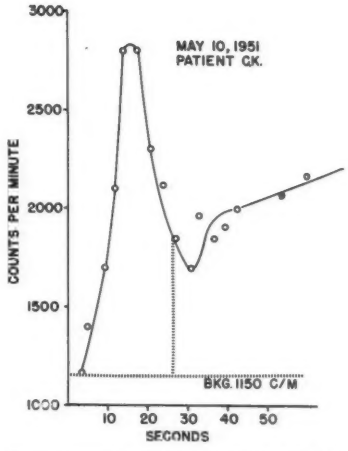


FIG. 3 *Left.* Cardiac output dilution curve obtained by posterior focusing on aortic arch. Note post-primary influx following primary circulation curve.

FIG. 4 *Right.* Dilution curve obtained from external counter focused over femoral artery. Note the rise due to accompanying venous return geometrically close to arterial flow.

withdrawn. If a 10 minute mixing time is observed before withdrawal, this volume would in most cases clinically approximate the blood volume.

The use of V_d as a calibration factor is valid, however, regardless of when it is withdrawn or whether final complete mixing has or has not been reached. Since the first term of this equation is a ratio, it is seen that the specific activity at final dilution, c_t, may be expressed in terms of counts per minute and the dilution curve expressed with an ordinate of counts per minute. This formulation is not required when the arterial flow is externalized and led past the detector, since the response of the detector to a known concentration of radioactivity may be easily ascertained. For an in vivo measurement, however, the complex geometric system cannot be duplicated for calibration, and thus it is necessary that the response of this complex system to a known concentration of radioactivity be accurately determined.

CALIBRATION OF DILUTION CURVE

The use of a calibration factor to relate counting rate to dilution may be valid only when the condition is imposed that the ideal mixing pool be observed by the detector during the primary circulation curve, as is observed at the time of calibration. If the observed pool has some later component that comes into the region after the period of primary circulation, the calibration described will be falsely high and the counting rate ratio in equation 3 will not be accurate.

This formulation is not confined to radioisotope technics but occurs in all cases of in vivo measurements where the complex geometric system cannot be duplicated for calibration and where it is necessary that the response of this complex system to a known concentration of injected material be accurately determined. For example, Milnor et al.,[13] using the ear for measurement of cardiac output by the injection of T 1824 dye, calibrated their system by arterializing the ear pinna and focusing the detector on the same site for the primary curve as for the final dilution.

Since it is rarely possible to select a site that has no return flow, the usual solution for this calibration has been to maximize the ratio of volume of direct arterial flow to vein and capillary volume. It is thus necessary in all external counting technics that curves be recorded from sites into which there will be minimal additional flow after the primary flow has been recorded.

This problem of calibration has been illustrated in the following dilution curves. Figures 1 and 2 show dilution curves obtained by a successful recording from a highly collimated scintillation counter, focused over the right heart and aortic arch respectively. A considerable number of such single-phase dilution curves were recorded from a posterior focusing on the aortic arch. These curves have shown no interference or later rise from other chambers, and have allowed the calculation of reasonable values of cardiac output.

Unsuccessful curves from over the aortic arch as well as from over the femoral artery are shown in figures 3 and 4. Although each primary curve is fairly well defined, the general upward inclination following the primary curve shows the presence of later components or post-primary influx. In each case the detector has recorded activity from a volume of venous return that is of sufficient magnitude to invalidate completely the calibration of the curve. These curves indicate that the final level was not obtained from the same geometric sampling volume as the primary circulation curve. This was the difficulty with the femoral artery curve, with its accompanying large venous return (fig. 4), and is a constant danger of any highly collimated technic in which such a small volume of the primary mixing pool is measured that any additional volume may account for a large percentage error.

This problem does not preclude the recording of successful dilution curves by use of high collimation. We have discarded this method only because the requirement of critical placement has been too extreme with patient variability to be successful for routine clinical application.

In the following studies it was considered that successful calibration was attained if no rise is seen in the record immediately following recirculation. If the record remains level or falls, it is improbable that an appreciable component of venous or capillary flow was measured. This standard is empirical, and actual verification rests on the correlation with cardiac outputs calculated from with-

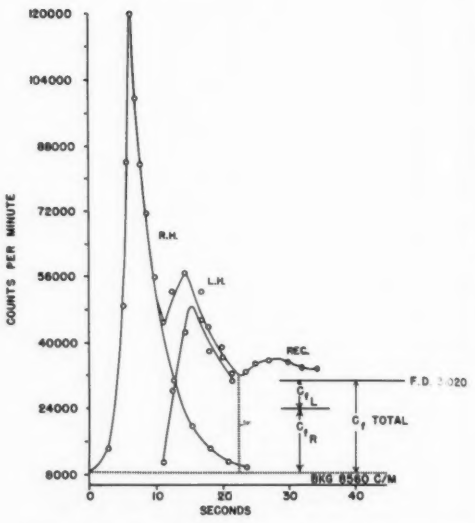


FIG. 5. Dilution curve obtained by counter receiving contributions from both chambers (dominant right heart). Ratios of final dilution represent the ratio of measured areas of right and left heart. Note that extrapolation line is due mainly to left chambers. Half time clearance of right chamber was 2.8 seconds, with 6.8 seconds for the left. Extrapolated area was 19 per cent of total area. REC = recirculation curve; F.D. = final dilution; R.H. and L.H. = right and left heart.

drawn samples.[12] It has been our practice to maintain the counter focused continuously over the site during the active measurement. For calibration, the in vitro blood has been withdrawn at a time sufficiently long after injection (10 to 15 minutes) that relative equilibrium has been reached. If the counting rate at this time of withdrawal levels off at a value less than the counting rate immediately following the primary curve, calibration requirements are considered as having been satisfied.

Analysis of Multichamber Technics

For a greater ratio of the volume of direct arterial flow to vein and capillary volume a wider collimation has been utilized with placement closer to the chest wall. Since such wider collimation and focusing results in recording from multiple dilution sites, attention must be given to the extension of the g

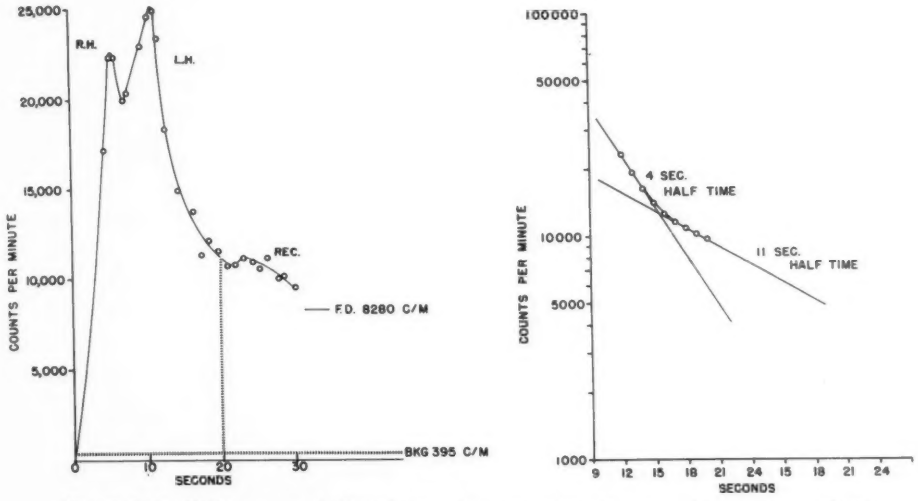


FIG. 6. *Left,* Dilution curve obtained by counter focused directly over mid-precordium. *Right,* Extrapolation line shows 2 components of 4 seconds and 11 seconds due to right and left heart clearance. Extrapolation area corresponds to 35 per cent of total area.

eral cardiac output formula to more than one chamber.

If 2 recorders are recording the counting rate individually from the right and left chambers of the heart, equation 3 will give

$$F A_r = c_{t_r} Vd \quad (4)$$

$$F A_l = c_{t_l} Vd \quad (5)$$

In this case A_r, c_{t_r} refers to the dilution curve areas and final concentration of the right heart alone with similar nomenclature for the left heart. Since the same flow, F, goes through both sides of the heart, the sum of these 2 equations, or of any number of flow sites, may be consolidated to give the general equation:

$$F = \frac{c_{t_r} + c_{t_l} + \ldots c_{t_n} V}{A_r + A_l + \ldots A_n} \quad (6)$$

Equation 6 states that if a dilution curve is recorded from a source of 2 or more sites, the output may be calculated by measuring the area of the total dilution curve, provided the calibration line is obtained with the identical geometric relationship to these same sites. This has been stated in a slightly different way by Veall et al.[6]

A curve recorded from more than 1 chamber is shown in figure 5. The extrapolation of the descending line of the right heart allows the dilution of the left heart to be separated, and the ratio of dilution areas of the right and left sides to be determined as shown by the ratio of final dilutions. For calculation of the cardiac output, however, all that is required is a complete measurement of the 2 phase curve as calibrated with the total final dilution.

Problems of Extrapolation

In evaluating the complete curve of primary dilution, exponential clearance has been generally assumed.[14] While Dow[15] and others have pointed out that this may not be entirely valid, it is still sufficiently accurate for clinical determinations and is generally used for quantitation of cardiac output by the dilution method. This assumption is valid, however, only for pure arterial flow occurring in a single time relationship. For this reason, the early part of this investigation was concerned with the attempted isolation of one or the other primary chambers. Such isolation avoided the complication of extrapolating the descending dilution curve when it had a multichamber time-phase relationship. Although

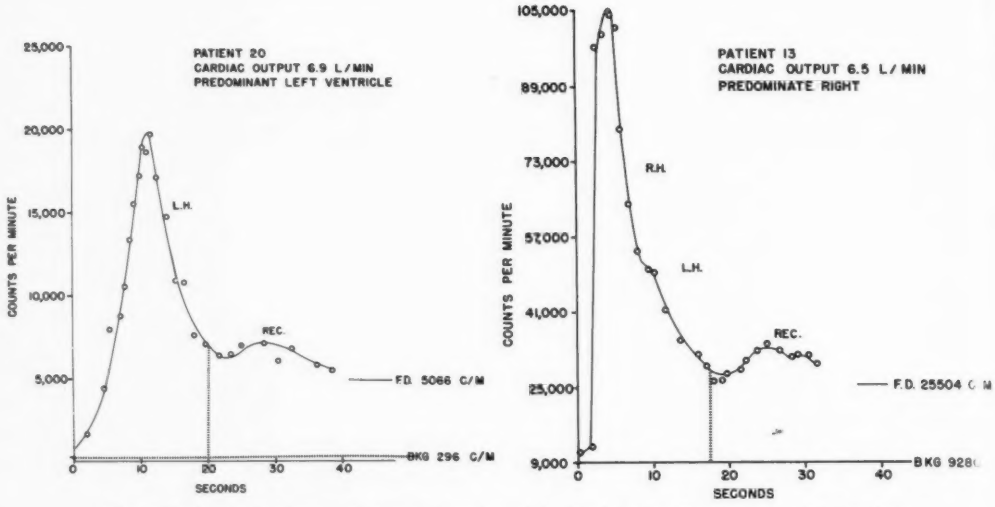


FIG. 7 *Left*. Predominant left heart focusing with calculated cardiac output of 6.9 L./min. Ratio of extrapolated area to total area is 30 per cent with half time of extrapolated line equal to 6.5 seconds.

FIG. 8 *Right*. Predominant right heart focusing with calculated cardiac out of 6.5 L./min. Ratio of extrapolated area to total area is 22 per cent. Half time of clearance is 5.5 seconds.

the assumption of an exponential clearance of the large chambers of the heart has been in reasonable agreement with observations, the summation of 2 or more time-phase curves is not exponential and can cause considerable departure from a semilogarithmic straight line.

This departure is illustrated in figure 6, which was obtained by a counter focused directly over the mid-precordium. The descending line in this case can be resolved into 2 components: one ascribed to the right heart and one ascribed to the left heart. The disadvantage of this type of curve is the difficulty in obtaining sufficient points to predict with reasonable accuracy the latter extrapolation. Since the extrapolated area is commonly 20 to 40 per cent of the total area, a few seconds' variation in clearance time may cause the calculation of output to be considerably in error. It has been necessary, therefore, to avoid any precordial site that would exhibit roughly equivalent contributions from the 2 chambers.

Our approach has been to select preferentially either one dominant chamber or the other so as to obtain a reasonably long period of single-phase extrapolation. In figure 7, a predominant left heart focusing is shown and in figure 8 a predominantly right heart curve is illustrated. In both cases the line of extrapolation is sufficiently long for accurate prediction. Thus, 2 criteria have been followed in this work. The first is to maximize a single-chamber clearance so as to keep the extrapolated area at a minimum and the second is to obtain as many points on the descending portion of the final dilution curve as possible.[12] If these conditions are observed, the choice of placement is secondary and may be made to fit the specific geometric configuration at hand.

DISCUSSION

Since the formulation of the Stewart-Hamilton equation for the calculation of cardiac output is general, it is not surprising that successful output measurements may be obtained by the external focusing of a detector over many dilution sites after the injection of a radioactive material into the circulating blood. This investigation has shown only a few of the possible sites.

Of more importance, however, in the extension of these measurements to external technics is the observance of the 2 necessary conditions of this formula. The first is accurate calibration of the dilution curve and the second is the reasonable assumption of exponential clearance from the extrapolation of the dilution curve. It has been the purpose of this report to point out the difficulties of curve calibration with highly collimated counters and the problem of successful extrapolation when multichamber technics are employed.

Since the cardiac configuration is extremely variable from patient to patient, successful clinical application of this technic must not depend upon critical placement. If the site of placement is not constant, highly collimated technics may be difficult, and multichamber recording must be considered. It has been demonstrated that this latter may be most successful if 2 criteria are followed. The first is adequate extrapolation of the curve from the final clearing chambers. This is most easily obtained by accentuation of the radioactivity arising from the chambers of one side of the heart so that the contribution of the other chambers will not appreciably distort its final extrapolation. Secondly, because of the inherent uncertainty of the character of the extrapolated line, it is desirable to make the measured area as large as possible, so that errors arising from the extrapolated area will be at a minimum. If these conditions are observed, the choice of placement is secondary and may be made to fit the specific geometric configuration at hand.

Summary

The extension of the measurement of cardiac output by external detection of iodinated (I^{131}) human serum albumin has been described. The problems of calculating a single-chamber dilution curve are discussed and the technic of obtaining successful extrapolation of multichamber dilution curves has been considered.

Independence of placement with these technics is emphasized and examples are shown of similar outputs obtained at completely differing focusing angles.

Summario in Interlingua

Es describite le extension del mesuration del rendimento cardiac per le detection externe de albumina iodate (I^{131}) in le sero human. Es discutite le problemas de calcular curvas de dilution a camera unic. Es etiam prestate attention al technica de obtener un valide extrapolation de curvas de dilution a plure cameras.

Es sublineate le independentia del placiamento in le uso de iste technicas. Exemplos es presentate de simile valores de rendimento cardiac obtenite per medio de completemente differente angulos focal.

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Medical Eponyms

By Robert W. Buck, M.D.

Ayerza's Disease. This symptom complex was first described by F. C. Arrillaga of Buenos Aires, a former pupil of Professor Abel Ayerza at the Hospital de Clinicas in that city, in an article entitled "Selerosis of the Pulmonary Artery Secondary to Certain Chronic Pulmonary Conditions (Black Cardiacs)" (*Scélerose de l'artère pulmonaire secondaire à certains états pulmonaires chroniques (cardiaques noire)*, which appeared in the *Archives des Maladies du Coeur des Vaisseaux et du Sang* **6**: 518-529, 1913.

"On August 20, 1901, Professor Ayerza (of Buenos Aires) demonstrated a patient in whom a peculiar form of cardiac insufficiency had drawn his attention. Struck by the color of this patient, he had called him a *black cardiac*. The pathological anatomy of these forms of illness never having been described, the present study will attempt to fill this gap, by presenting the complete picture of the disease as it appeared in eleven cases together with radiographic pictures . . . It nearly always affects subjects who have not yet passed their fifties . . . They have chronic disease of the respiratory tract going back ten, twenty, or even twenty-five years . . . they are emphysematous. It is this condition which eventually secondarily involves the pulmonary artery, causing it to become selerotic, and the heart, leading to its hypertrophy . . . The sign which first attracts one's notice in examining the patient is the *cyanosis*."

The Determination of Cardiac Output by the Dilution Method without Arterial Sampling

II. Validation of Precordial Recording

By Walter H. Pritchard, M.D., William J. MacIntyre, Ph.D., and Thomas W. Moir, M.D.

Technics for determining the cardiac output by recording the dilution curve of injected iodinated I^{131} human serum albumin from precordial sites have been described. By viewing predominantly either the right or left side of the heart and by rapid delivery of the isotope, quantitation of the dilution curves for cardiac output has been possible without critical requirements for placement of the counter. In a series of 26 determinations in normal patients cardiac output values calculated from simultaneously recorded precordial curves and withdrawn arterial blood showed an average agreement within ± 8 per cent. In a smaller series of 8 determinations on patients in heart failure, an average deviation of ± 9 per cent was found.

IN THE accompanying paper[1] we have pointed out the necessary theoretical requirements for calculating cardiac output from precordial dilution curves and stated that accurate calibration and extrapolation of the curves are the prime requisites for successful quantitative measurements. In external counting technics, accurate calibration of the curve can be obtained only if the final dilution level is recorded from the same geometric sampling area as the primary dilution curve, so that effects of post-primary influx are minimized. Extrapolation problems can be resolved best by maintenance of a sufficiently high counting rate to record as great a number of clearance points as possible, and by reducing to a minimum the ratio of the extrapolated area to the measured portion of the dilution curve. In this paper we discuss the technics that during 7 years of study have been found necessary to or helpful in ensuring the accuracy of the radiocardiogram as a tool in the determination of cardiac output.

From the Departments of Medicine and Radiology, University Hospitals and Western Reserve University, Cleveland, Ohio.

These studies were supported by gifts from the Ford Engineering Co., and Oglebay Norton Co., Cleveland, Ohio, and by a grant, A. E. C. Contract No. W31-109-eng-78, with Western Reserve University.

Methodology and Technics

Recording instruments were used, consisting of a scaler, Esterline-Angus recording meter,* and a Berkeley† counting rate computer, whose scale was modified to record at intervals of from one third to 1 second. The scintillation counter was shielded, but further collimation of the heart was necessary and several types of collimators were explored for adaptation to this method.

Early in the work, when we attempted single-chamber recording, small-holed (¼″ to ½″ in aperture diameter and 4″ in length) collimators were used. With the low efficiency and high target effect, the recording of good curves required that counter placement be critical. Prior to recording the precordial curve the patient was fluoroscoped, and a coin was placed over the desired spot on the precordium. Following the radiocardiogram a chest x-ray was taken with the patient in approximately the same position. Figure 1 shows the areas of the optimum sites from which good curves were obtained in many trials. This diagram suggested that good curves could be recorded from the mid-lower portions of both sides of the precordium. Curves taken from high or extremely low positions on the right side were poor. In spite of careful fluoroscopy, for a reasonably accurate placement, positioning of the counter introduced errors in the calculation of flow largely because of the difficulties in eliminating the post-primary influx. For this reason the approach of heavily collimated, critical placement was abandoned.

*Esterline-Angus Co., Inc., Indianapolis, Ind.

†Model 1600, Berkeley Scientific Co., Richmond, Calif.

Collimation

In general, with collimation we attempted to match the dominant chamber to be viewed in respect to its anatomic location beneath the chest wall while restricting to a minimum radiation from extraneous sources. Figure 2 shows the dimensions and efficiency characteristics of 2 collimators tested. The plots of superimposed curves represent the counting rate efficiency recorded from a radioactive point source moved perpendicular to the axis of the collimator at varying distances from the aperture. The collimator on the left was used in the majority of the studies reported in this paper and was found satisfactory, that on the right is of the highly collimated type used previously for single-chamber determinations.

Placement of Counter

Although dilution curves can be inscribed from varying sites over the precordium and posterior thorax, curves from which quantitative cardiac output values can be accurately calculated must meet certain criteria. From theoretic considerations, when multichamber recording is desired, either the right or left heart dilution should be emphasized and the contribution of the other side minimized.

Curves recorded from the mid-precordium showing approximately equal diluting volumes between the right and left sides of the heart are usually unsatisfactory. The disadvantage of these curves lies in the uncertainty of predicting the final extrapolation. Since such curves exhibit the summation of 2 clearance chambers of completely different exponential rates, this summation will not be a simple exponential decline, so that extrapolation on this basis will not be valid.[1]

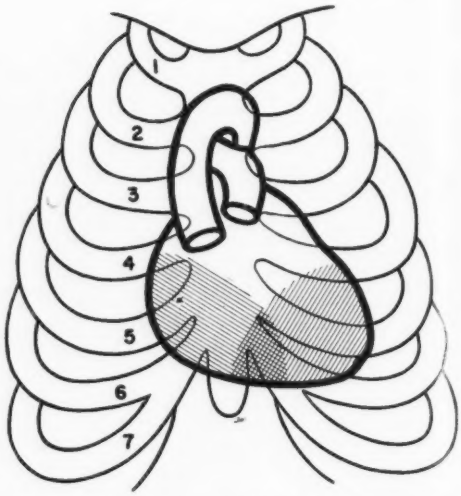


FIG. 1. Diagram of precordium. *Lined areas,* satisfactory curves recorded with highly collimated system. *Crossed area,* double peak curves even with high collimation.

Although positioning of the counter to accentuate the dilution curve from one side of the heart is essential for good quantitation, each side of the heart offers its peculiar advantages. From the

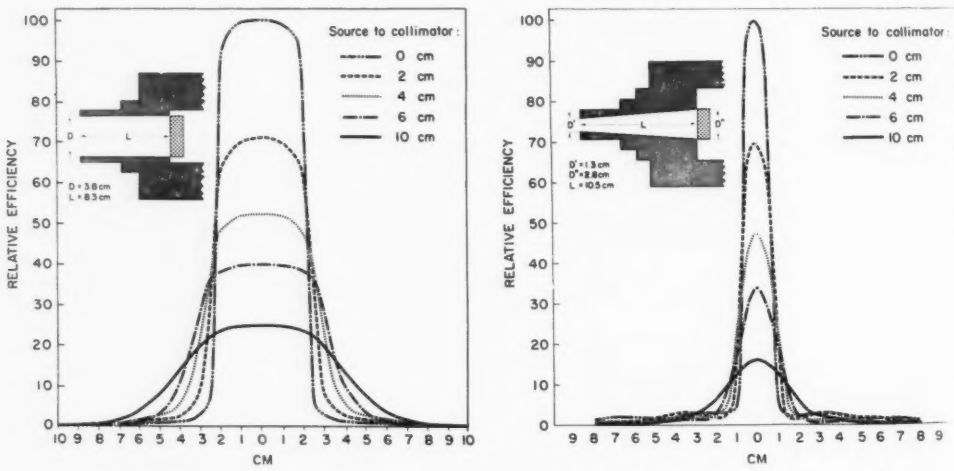


FIG. 2. Dimensions and efficiency characteristics of 2 types of collimators representing moderate (*left*) and high (*right*) collimation. Left collimator was used in the correlation study and right collimator was utilized for earlier single-chamber attempts.

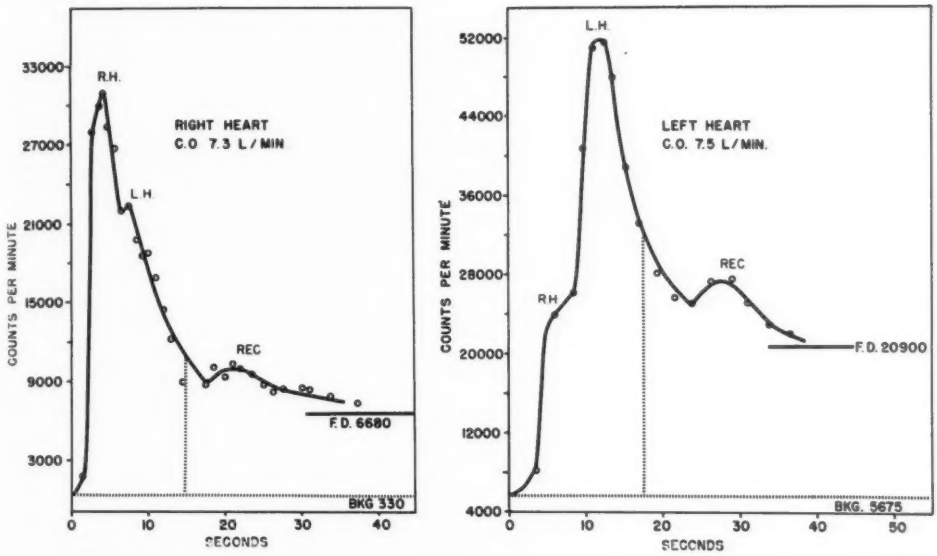


FIG. 3. Precordial output curves recorded in same patient with counter focused over right and left precordium. *Dotted vertical intercept* from descending limb to time axis separates measured from extrapolated area of curve in each. Notations on curves refer to contributions from left heart (L.H.), right heart (R.H.), and recirculation (REC). Correlation with curves based on withdrawn arterial blood was 10 per cent. C.O. = cardiac output; F.D. = final dilution, and BKG = background in counts/minute.

right side there is a higher concentration of relatively undiluted radioactive material, giving increased sensitivity, a large ratio of the measured to extrapolated portion of the curve, and usually a short but definite final extrapolation line. Recording from this side however, has the disadvantage that possible poor mixing may be unrecognized and abnormally high values may be recorded. The left side offers the advantages that there are usually more recorded points on the descending limb of the curve for extrapolation, mixing problems are minimal, and from a clinical point of view more heart diseases are associated with left-sided enlargement and more discrete left chamber separation is thus possible. On the other hand, the left side has the disadvantage of lower sensitivity in the counting rate due to dilution and distance, and the extrapolated area is usually greater than from the right.

In figure 3 are shown 2 curves of the same patient recorded from each side of the precordium with values of cardiac output that are almost identical. From the right side there is an abrupt, early, rapid rise to a maximal value within a few seconds followed by a rapid decline in concentration which is interrupted on the descending slope by a small deviation and a further fall at a slower rate. This latter slower portion of the curve indicates clearance of the left chambers, and its size in proportion to the whole curve depends upon the amount of left chamber viewed by the counter in this position. This left heart contribution is usually easily distinguishable from the final surge due to recirculation of the injected isotope.

In curves from the left side the initial onset may be rapid and abrupt, but after a small primary rise a succeeding larger, steep curve reaching a peak later on the time axis is seen. Then follows a smooth, uninterrupted descent as clearance from the left side continues before the recirculation wave is identified. In none of the curves recorded from either side of the heart have we been able to identify small waves of activity on the descending limb indicative of coronary circulation effects.[2]

A serious source of error in placement of the counter may arise whenever the counter is focused over the higher portions of the right inflow tract, i.e., superior cava or high right atrium. In this situation, the counter does not view a homogeneous concentration and thus records abnormally tall, steep, narrow, single-phase curves. These curves are indicative of a strong radioactive source which has not been diluted by a mixing process and exhibits laminar rather than turbulent flow. Because of the narrowness of these curves, the area is small and quantitation will usually result in

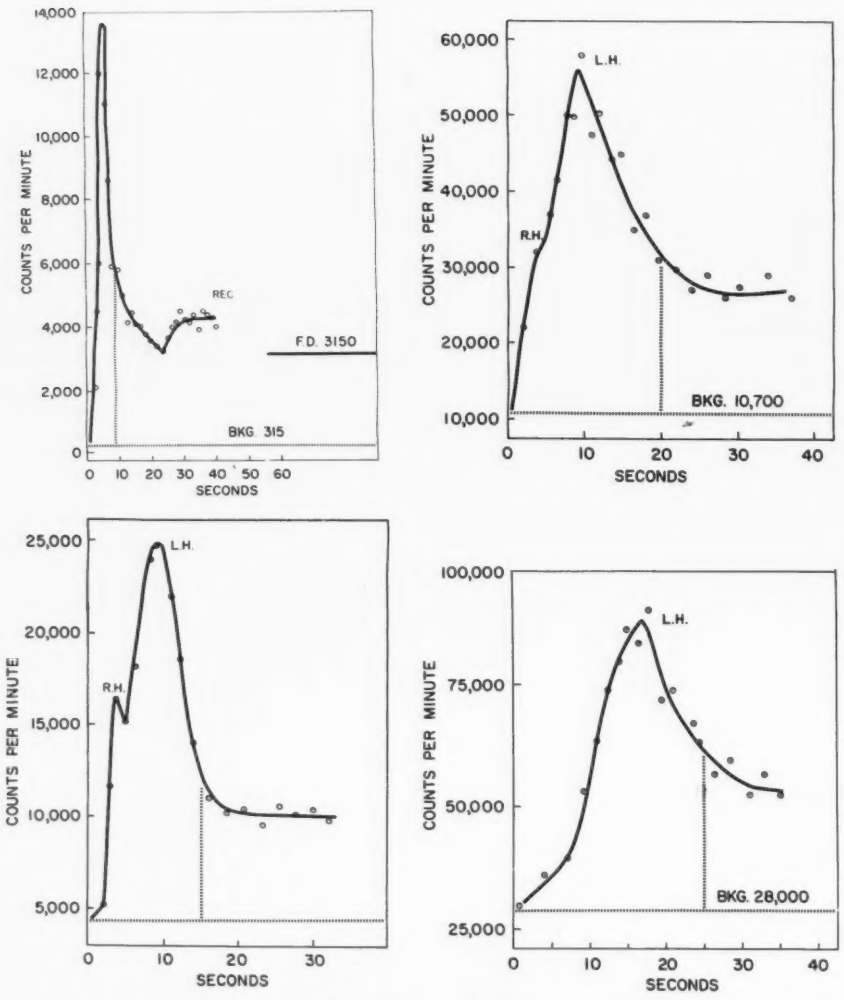


FIG. 4 *Top, left.* Curve recorded from high right inflow tract (right atrium or low superior vena cava) indicative of poor mixing of highly concentrated injected isotope. Note tall, narrow, brief monophasic curve. External calculated output 10.8 liters/minute compared to 4.0 liters/minute from withdrawn arterial dilution curve.

FIG. 5 *Bottom left, top right, and bottom right.* Curves from same patient recorded at same precordial site following different types of injection. Note successive "smearing" of curve with slower injection rates. *Bottom, left,* Calculated cardiac output is 7.4 liters/minute; *top right,* 6.7, and *bottom right,* 6.1. Half-time clearance of curves was 3.5, 9.3, and 10 seconds, respectively.

spuriously high calculations of cardiac output. Figure 4 illustrates the effects of recording from a point too high in the inflow system. The same type of error may be present if the injected substance is delivered into the left ventricle too close to the outflow tract via left atrial puncture, and concentrations are determined from sampling the blood of the peripheral arteries. Curves recorded from low positions on either side would exhibit in many instances contributions from other large vascular pools, such as the liver.

At the present time it is our practice, when-

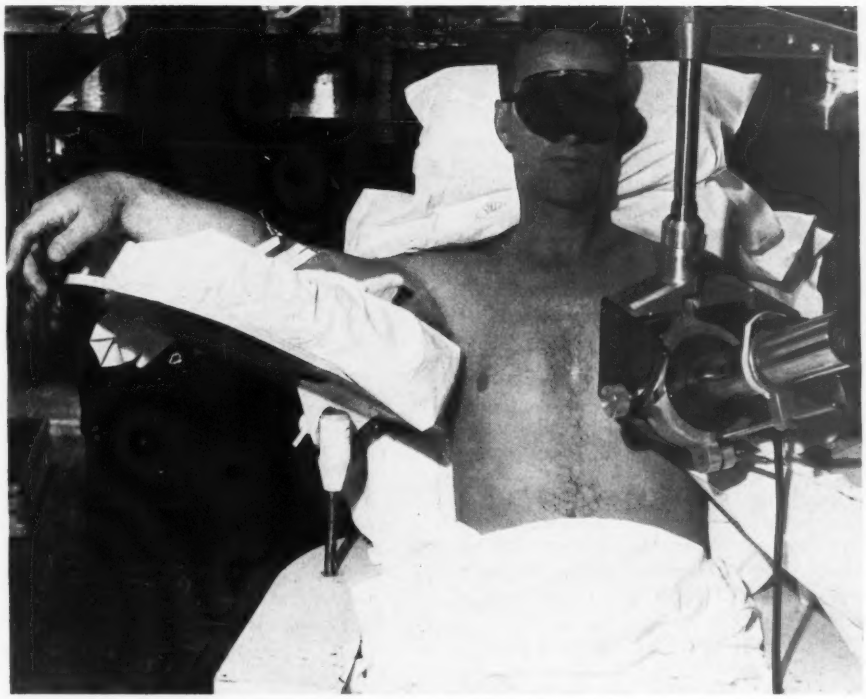


FIG. 6. Position of patient in laboratory chair with injection to be made in right arm and counter placed over left precordium. In correlation left brachial artery used as site of withdrawn samples.

right predominant curves are desired, to place the counter approximately perpendicular to the chest wall without lateral rotation over the fourth intercostal space or fifth rib at the right parasternal margin. To record left predominant curves the counter is usually placed at the point of the maximal apical impulse with the counter rotated somewhat medially, perpendicular to the chest wall. Minor placement variations may be made depending on the chest contour and the heart size. Empirically, in thin people with centrally located hearts we have found the right predominant curve more satisfactory, and in the more obese, stocky person the left predominant curve appears preferable.

Delivery of Isotope

Early in our studies it became evident that not only did the site of precordial recording and type of collimation affect the radiocardiogram, but also the type of delivery of the isotope into the circulation had a significant influence on the form of the recorded curve. Figure 5 illustrates the effects of the volume injected and of flushing on curve form. These curves were obtained over the same left precordial site on a normal subject within a few minutes of each other. The volume injected and the rate of delivery were varied and the results are representative of other similar trials. In figure 5, bottom, left, the usual technic was followed, of a 3 ml. volume followed by a 10 ml. saline flush. A "normal" left predominant curve resulted.

In figure 5, top, right, the same volume without a flush resulted in a less discrete curve; the summit is not displaced in time, but the final slope of clearance is slower. In figure 5, bottom, right, an 8 ml. dose without a flush gave a slower rise, a summit displaced later in time, and a much delayed final clearance.

Flushing acts as much to compress the trailing end of the volume injected into a smaller bolus as to speed its entrance into the right heart. Although the form of the curve should theoretically make little difference in its quantitation, from a practical consideration the rate and degree of fall of the final slope influence not only the accuracy of the extrapolation but also the percentage extrapolated to the total area. To obtain optimum characteristics of the curve we have found flushing to be of great importance. In figure 5 the per-

centages of extrapolated to total area (bottom left, top right and bottom right, respectively) are 17, 34, and 39. The larger the extrapolated area becomes, the less is the accuracy of the method.

The effects of position of the patient were also studied, and consistently good results were obtained by having the patient seated in a reclining chair with the arm into which the injection is to be made elevated and relaxed (fig. 6). Usually from 2 to 3 ml. labeled albumin containing a minimum of 5 μc. and a maximum of 180 μc. are rapidly delivered in 1 stroke, and followed immediately by a forced flush of 10 ml. saline through a 3 way stopcock. When the patient is recumbent, it is important to avoid axillary constriction. The arm should not be raised immediately after injection, as trapping at the thoracic inlet has frequently been encountered. Whenever repeated determinations at successive intervals over a short period of time are necessary, the dose of labeled albumin has been approximately doubled for each succeeding injection, to insure sufficient statistical accuracy over the previous background. This has limited the number of determinations that can be made at any one sitting, but better defined curves have resulted.

Procedure

For a test of the validity of our theoretical conceptions, a series of patients was studied in which the cardiac output values calculated from dilution curves recorded from the precordium were compared with simultaneously recorded curves obtained from blood withdrawn from the brachial artery.[3] The patients were allowed to rest quietly in the laboratory armchair, while a no. 18 Cournand needle was inserted into the basilic vein of one forearm for injection and another Cournand needle was placed into the brachial artery of the other arm for recording the peripheral dilution curve, as described previously.[3] Since the previous report of our arterial puncture technic, improved sensitivity of recording has been obtained by the use of a channeled* sodium iodide crystal through the center of which is inserted a siliconed stainless-steel tube. Successful curves recorded with this channeled crystal have been obtained with only 20 μc. of labeled albumin. From 20 μc. to 120 μc. contained in a 2 to 4 ml. volume were rapidly injected and followed by the usual 10 ml. saline flush. Both curves were continued until well after the primary circulation, to insure the identification of any post-primary influx on the precordial curve and to identify recirculation on both curves. Thus one could compare accurately a precordial curve with the dilution curve of withdrawn arterial blood. It had been shown previously in this laboratory that arterial dilution curves recorded in this manner checked well in animals[4] when compared to measurements obtained with aortic rotameters and in man when compared with cardiac outputs obtained by cardiac catheterization.[3]

*Model AF, Harshaw Chemical Co., Cleveland, Ohio.

TABLE 1.—*Correlation of Cardiac Output in Normal Patients*

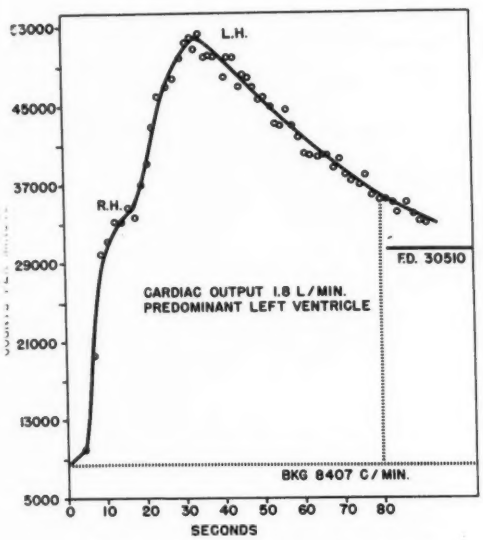
Patient no.	Predominant chamber	Precordial cardiac output (L./min.)	Arterial cardiac output (L./min.)	Deviation from arterial cardiac output (%)
1	R	3.4	3.4	0
2	R	6.2	7.1	−13
	L	5.8	5.9	−2
3	L	4.9	4.7	+4
	L	5.0	5.3	−6
4	R	5.8	6.0	−3
	L	4.7	4.8	−2
5	L	5.0	5.2	−4
	L	5.6	5.3	+6
6	R	7.3	6.6	+10
7	R	6.3	6.2	−2
8	R	5.2	4.9	+6
	L	6.1	5.3	+15
9	R	7.4	7.7	−4
10	R	6.0	6.4	−6
12	L	4.9	5.1	−4
13	L	6.5	5.8	+12
	R	6.6	5.8	+14
14	L	7.2	6.4	+11
16	R	4.5	4.4	+2
	L	5.0	4.2	+19
17	L	6.1	6.2	−2
	L	5.3	4.7	+11
18	L	6.9	5.4	+28
	L	8.6	8.3	+4
20	L	6.9	7.4	−7
	L	6.2	5.6	+11

Average deviation ±8%.

RESULTS

Normal Subjects

In 17 patients, 26 determinations were performed, of which 10 were right predominant curves and 16 were of the left predominant type. In table 1 are shown the data from the entire series of patients not in heart failure. The range of cardiac output values was from 8.3 liters per minute to 3.4 liters per minute, with correlation deviations of the precordial from the arterial curve of from minus 13 to plus 28 per cent, with an average of ±8 per cent. In this laboratory previous correlations of the arterial dilution curve with the standard Fick procedure with patients in the basal



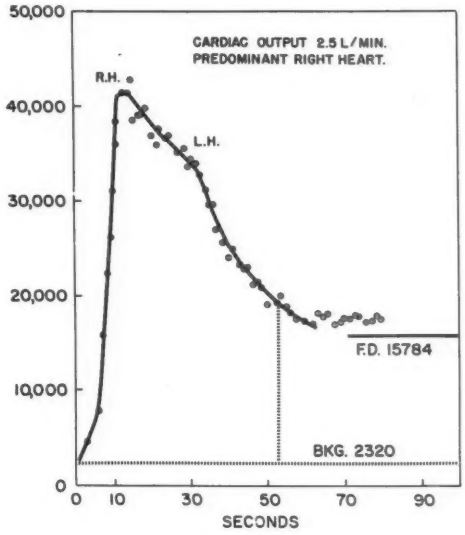


FIG. 7 *Left.* Precordial curve, left predominant type, of patient in severe congestive heart failure. Note greater number of recorded points due to higher counting rate and slow flow. Ratio of extrapolated area to total area is 50 per cent. Half time of clearance is 66 seconds.

FIG. 8 *Right.* Precordial curve, right predominant type in patient with severe congestive heart failure. Ratio of extrapolated area to total area is 36 per cent. Half-time clearance is 30 seconds.

state have shown an average deviation of ±8 per cent between the Fick and dilution output calculations. In this series no attempt was made to maintain a constant basal state, and several patients were studied in the afternoon after lunch. Thus, since the first and second runs in patients of this series were not expected to be the same, the second trial served as a separate determination of comparison between the precordial and arterial values rather than a comparison of the 2 separate runs against each other. Maintaining good flow through the arterial needle of the brachial puncture after some time had elapsed in the study was a problem in the occasional case and may have accounted for the larger errors in which the precordial value exceeded the arterial value. The abnormally large deviation in patient no. 18 has been attributed to this cause.

Cardiac Patients

Although fewer studies have been performed on patients in severe cardiac failure, our results have been as satisfactory as those in the normal group. A typical dilution curve from the left side is shown in figure 7 and illustrates the characteristic slow dilution and long extrapolation required when the cardiac output is low. Because of the tendency of the downstroke of the primary curve to merge with recirculation, fast injection, rapid flushing, and adequate isotope doses are necessary

TABLE 2.—*Correlation of Cardiac Output in Cardiac Patients*

Patient no.	Predominant chamber	Precordial cardiac output (L./min.)	Arterial cardiac output (L./min.)	Deviation from arterial cardiac output (%)
15	R	2.5	2.3	+9
	L	2.2	2.2	0
19	L	3.1	3.4	−9
	L	3.3	3.2	+3
21	L	2.5	2.0	+25
	L	1.8	1.6	+12
22	L	2.9	2.9	0
	L	2.8	3.1	−10

Average deviation ± 9%.

TABLE 3.—*Correlation of Cardiac Output (All Determinations)*

Range of deviation from arterial cardiac output (%)	No. of determinations
0—4	15
5—10	9
11—17	9
Over 17	2

to give high statistical accuracy in recording the descending slope.

Table 2 shows compilation of 8 runs on 4 patients in cardiac failure. It should be noted that the left chamber has been selected as the site in most instances, although figure 8 demonstrates that it is possible to record from the right chamber with adequate reliability.

In table 3 are summarized all data, from both normal subjects and subjects with cardiac disease, in a condensed fashion; it can be seen that only 2 of 35 determinations show deviations over 17 per cent.

CONCLUSIONS

If the analytical considerations can be fulfilled, and the counter can be placed on the precordium in such a way as to emphasize a predominant chamber, successful clinical studies of cardiac output can be made independent of critical placement of the counter. The necessary precautions have been described to accomplish this, and correlation studies in patients showed a high degree of accuracy when cardiac output values obtained by this method were compared with those calculated from peripheral arterial dilution curves.

SUMMARY

Technics have been discussed that are important in recording precordial dilution curves from which cardiac output values can be calculated.

Proper placement of the counter is important, but is not critical, so long as the right or left side of the heart is made predominant and the effects of the other chamber are minimized.

In a series of patients the precordial curves are compared with curves obtained by brachial artery puncture; good agreement was obtained with an average deviation of the precordial from the arterial curves of 8 per cent.

This technic may be a useful adjunct in the study of cardiovascular diseases, since it involves very little cooperation from the patient and determinations can be made with ease.

SUMMARIO IN INTERLINGUA

Es discutite technicas de importantia in le registration de precordial curvas de dilution como base del calculation del rendimento cardiac.

Le correcte placiamento del contator es importante sed non de importantia critic, si predominantia es attribuite al latere dextere o al latere sinistre del corde, con minimisation del effectos del camera al latere contrari.

In un serie de patientes le curvas precordial esseva comparate con le curvas obtenite per punctura del arteria brachial. Le concordantia esseva bon, con un deviation medie del curva precordial ab le curva arterial de 8 pro cento.

Iste technica va possibilemente esser un adjuncto utile in le studio de morbos cardiovascular, proque illo require pauc cooperation del parte del patiente, e le determinationes se face con facilitate.

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Graded Pulmonary Vascular Changes and Hemodynamic Findings in Cases of Atrial and Ventricular Septal Defect and Patent Ductus Arteriosus

By Donald Heath, M.D., H. Frederic Helmholz, Jr., M.D., Howard B. Burchell, M.D., James W. DuShane, M.D., and Jesse E. Edwards, M.D.

With use of a previously described system of grading, a study was made of the relation between each of the grades of hypertensive pulmonary vascular disease and the hemodynamic findings in the lesser circulation in 15 cases of atrial septal defect, 19 cases of ventricular septal defect, and 6 cases of patent ductus arteriosus.

IN A previous paper[1] 6 histologic grades of hypertensive pulmonary vascular disease were defined on the basis of study of 67 cases of congenital septal defect of the heart and 2 cases of idiopathic pulmonary hypertension. In 40 of these 67 cases of atrial or ventricular septal defect or patent ductus arteriosus, detailed physiologic studies had been carried out. These data are now employed to demonstrate the relation of each grade of the suggested pathologic classification to the level of pulmonary arterial blood pressure and flow and to age. In many instances the physiologic data were obtained while the patient was breathing air and 100 per cent oxygen respectively. Similar data from 3 cases of idiopathic pulmonary hypertension, 2 of which were included in the previous paper, are included for purposes of comparison.

Methods and Material

Forty cases were studied and these were subdivided into 2 groups according to the type of septal defect present.

The first group consisted of 15 patients with interatrial communication (cases 1 to 15). Their ages ranged from 10 to 55 years. Patients 1 to 8 had an atrial septal defect of the foramen ovale type as the sole congenital defect. Patients 9 to 12 had a partial anomalous pulmonary venous connection in association with an atrial septal defect, usually located in the upper part of the atrial septum, as described by Swan and his associates.[2] Patients 13 and 14 each had a partial common atrioventricular canal (that is, with no interventricular communication). Patient 15 had an unusual form of atrial septal defect in which the evidence indicated that the pulmonary hypertension had been present from birth. The age, sex, diagnosis, and grade of hypertensive pulmonary vascular diseases of each of these patients are shown in table 1.

The second group consisted of 25 patients with congenital heart disease characterized by a large interventricular communication (cases 16 to 20 and 22 to 35) or a wide patent ductus arteriosus (cases 36 to 41). The ages of the patients in this group ranged from 10 months to 46 years. The age, sex, additional malformations, and grade of hypertensive pulmonary vascular disease of each of these patients are shown in table 2. In only 1 patient (case 17) was pulmonary stenosis present, and it was of mild degree.

No patients with congenital or acquired mitral stenosis were studied, but 3 additional patients with idiopathic pulmonary hypertension (cases 42 to 44) were included for purposes of comparison.

The physiologic data were obtained by catheterization of the right chambers of the heart and the pulmonary arteries, and by puncture of systemic arteries. The blood pressures and the data on oxygen saturation in the pulmonary and radial arteries, together with the oxygen consumption in cubic centimeters per minute, were measured while

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TABLE 1.—*Group 1 Cases. Grade of Hypertensive Pulmonary Vascular Disease and Blood Pressures in 15 Cases of Interatrial Communication*

Case no.	Sex, age (years)	HPVD* (grade)	Arterial blood pressure in mm. Hg							
			Pulmonary				Radial			
			Mean		Systolic		Mean		Systolic	
			Air	100% O_2	Air	100% O_2	Air	100% O_2	Air	100%
Atrial septal defect of classic variety										
1	F41	1	22	15	34	24	113	112	160	157
2	F55	1	26	18	44	31	87	—	115	—
3	F41	1	28	24	52	44	76	77	120	120
4†	F46	1	30	20	44	42	75	60	101	95
5	F32	5	49	47	86	73	86	80	116	107
6	F54	3	56	—	101	—	92	—	124	—
7	F28	3	61	50	106	92	75	77	114	118
8†	F48	2	64	55	114	108	83	90	101	121
Atrial septal defect with partial anomalous pulmonary venous connection										
9	M10	1	33	19	50	36	76	85	110	119
10	M37	4	48	48	76	85	85	84	120	121
11	F46	5	49	45	90	79	90	91	127	117
12	F27	4	67	67	107	101	81	87	116	130
Common atrioventricular canal with no subvalvular communication										
13	F27	5	90	—	137	—	82	—	109	—
14	F20	1	48	45	81	73	86	91	111	114
Atrial septal defect with pulmonary hypertension probably present from birth										
15	M27	6	102	98	139	130	81	80	117	109

*HPVD, hypertensive pulmonary vascular disease.
†Associated mitral incompetence.

the patient was at rest and while breathing air and, in most instances, 100 per cent oxygen. In some instances only air or oxygen inhalation was employed (for example, cases 17 to 20). These data were used to calculate the pulmonary blood flow, the total pulmonary resistance, and the percentage intracardiac shunts in both directions.

Blood Pressure in Pulmonary Artery. The mean and systolic blood pressures in the pulmonary and radial arteries for each of the cases included in groups 1 and 2 are shown in tables 1 and 2 respectively. Normal values for pulmonary-artery blood pressure in millimeters of mercury were considered to be systolic 22, and diastolic 12. The mean blood pressure in the pulmonary artery was calculated by adding the diastolic pressure to one third of the pulse pressure, giving a normal value of 15 mm. Hg.

Pulmonary Blood Flow. The total pulmonary and systemic blood flows in liters per minute were calculated from the oxygen consumption and the arteriovenous oxygen difference in each of the 2 circulations, according to the following formula based on the Fick principle:

$$\frac{O_2 \text{ consumption (ml./min.)}}{O_2 \text{ content in artery} - O_2 \text{ content in vein (vol. \%)}} \times 10$$

To allow for the different sizes of the patients and obtain comparable values for pulmonary blood flow we used the pulmonary index of blood flow:

$$\frac{\text{Total pulmonary blood flow in L./min.}}{\text{Surface area in M.}^2}$$

We regarded the normal pulmonary index of flow as being in the range of 2.5 to 4.4 L./min./M.^{2}. (See reference 3.)

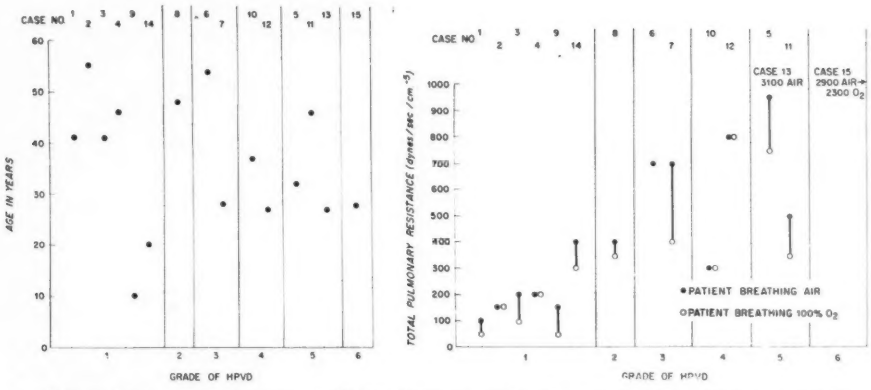


FIG. 1 *Left.* Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and age.

FIG. 2 *Right.* Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and total pulmonary resistance.

Pulmonary Resistance. Total resistances in the pulmonary and systemic circulations were calculated in dynes/sec./cm.$^{-5}$ according to the formula

$$\frac{\textit{Mean arterial blood pressure (mm. Hg)}}{\textit{Total blood flow (L./min.)}} \times \frac{(1{,}332 \times 60)}{1{,}000}$$

Arteriolar resistance was not calculated.

We regarded the normal total pulmonary resistance in older children and adults as being in the range of 90 to 300 dynes/sec./cm.$^{-5}$, with a mean value of 200 dynes/sec./cm.$^{-5}$, and the normal systemic resistance as being in the range of 750 to 1,600 dynes/sec./cm.$^{-5}$, with a mean value of 1,200 dynes/sec./cm.$^{-5}$. These mean values give a normal ratio of pulmonary to systemic resistance of 0.16.

Shunts Through the Congenital Defect. Percentage left-to-right and right-to-left shunts were calculated from the oxygen saturations[4] in the pulmonary artery (Spa), pulmonary vein (Spv), radial artery (Sa), and systemic veins (Sv) according to formulas:

$$\textit{Percentage left-to-right shunt} = \frac{\text{Spa} - \text{Sv}}{\text{Spv} - \text{Sv}} \times 100$$

$$\textit{Percentage right-to-left shunt} = \frac{\text{Spv} - \text{Sa}}{\text{Spv} - \text{Sv}} \times 100$$

RESULTS

Results in Group 1 Cases (Interatrial Communication). Figure 1 shows the relation between grade of hypertensive pulmonary vascular disease and age. In the cases of interatrial communication, grade 1 lesions were found alike in children (case 9) and adults more than 40 years of age (cases 1 to 4). No patient, however, with vascular changes included in the range of grades 2 to 6 was less than 25 years of age (cases 6 to 8, 10 to 13, 5 and 15). In those patients, usually more than 25 years of age, in whom pulmonary hypertension was found, structural changes were present in the pulmonary arteries. The lack of an obvious relation between age and grade of hypertensive pulmonary vascular disease in this group may well indicate that the duration of the elevated blood pressure in the pulmonary artery is not determined by the patient's age alone in interatrial communication.

Figures 2 and 3 show the relation between grade of hypertensive pulmonary vascular disease and pulmonary resistance. In the patients with interatrial communication there was a relation between the level of total pulmonary vascular resistance and the grade of structural changes in the pulmonary arteries. In 5 of the 6 patients with grade 1 lesions (cases 1 to 4, and 9) the resistance was normal at 200 dynes/sec./cm.$^{-5}$ or less, and in the sixth (case 14) it was 400 dynes/sec./cm.$^{-5}$. In patients with grade 3 lesions (cases 6 and 7) the resistance was 700 dynes/sec./

TABLE 2.—*Group 2 Cases. Grade of Hypertensive Pulmonary Vascular Disease and Blood Pressures in 19 Cases of Large Interventricular Communication and 6 Cases of Widely Patent Ductus Arteriosus*

Case no.	Sex, age (years)	HPVD (grade)	Associated anomaly*	Arterial blood pressure in mm. Hg: Pulmonary Mean Air	Pulmonary Mean 100% O_2	Pulmonary Systolic Air	Pulmonary Systolic 100% O_2	Radial Mean Air	Radial Mean 100% O_2	Radial Systolic Air	Radial Systolic 100% O_2
Large interventricular communication											
16	M2	2	O	34	—	82	—	66	—	89	—
17	F22	1	PS	44	—	63	—	80	—	116	—
18	M1½	1	O	45	—	69	—	57	—	88	—
19	M10/12	1	ASD	48	—	85	—	60	—	91	—
20	F1	1	ASD	—	48	—	78	—	55	—	76
22	F5	3	MI	53	39	73	70	48	46	72	74
23	M15/12	3	O	54	52	76	73	—	—	—	—
24	F15	1	MI	56	40	85	62	75	78	97	100
25	F10	1	O	64	54	89	77	74	73	96	94
26	M2	2	PDA	66	43	91	66	63	59†	89	82†
27	M3½	3	AVC	66	57	87	90	67	77	78	105
28	M1½	2	AVC	66	36	89	60	68	67	122	90
29	F11	1	O	69	52	98	83	77	74	101	95
30	F21	3	O	70	63	115	108	79	80	115	111
31	M13	1	T	70	—	100	—	77	74	114	109
32	F23	3	O	73	61	120	102	79	83	110	110
33	M24	3	O	73	66	108	111	81	82	117	119
34	F37	2	ASD	75	—	140	—	75	99	118	135
35	F17	5	O	87	85	127	124	100	102	159	158
Widely patent ductus arteriosus											
36	M21	5	O	48‡	—	129‡	—	92	—	117	—
37	M5	2	C	—	57	—	70	—	58	—	67
38	F10	3	O	76	—	101	—	77	—	105†	—
39	F20	5	O	81	75	106	89	73	72	99	100
40	F34	5	O	84	85	109	116	88	85	115	118
41	F46	5	C (mild)	102	96	145	140	91	95	145	151

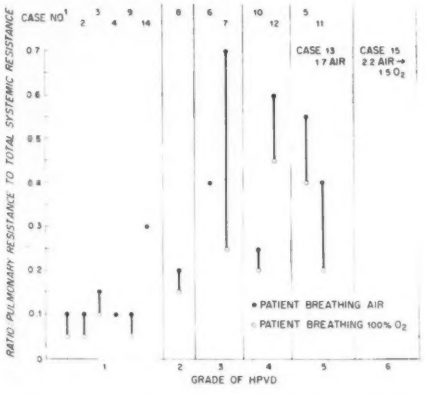
*O, none; ASD, atrial septal defect; PS, mild pulmonary stenosis; PDA, patent ductus arteriosus; C, coarctation of aorta; T, corrected transposition of great vessels; AVC, common atrioventricular canal; MI, mitral incompetence.

†Aortic blood pressure.

‡Right ventricular blood pressure.

cm.$^{-5}$, and in patient 15 with grade 6 lesions it was 2,900 dynes/sec./cm.$^{-5}$, all the figures quoted so far being obtained while the patients were breathing air. While, for the group as a whole, the total pulmonary resistance tended to rise with progressive vascular changes, there was variation in any one group of similar grade of structural change. Thus, 2 patients with grade 4 lesions had a resistance of 300 dynes/sec./cm.$^{-5}$ (case 10) and 800 dynes/sec./cm.$^{-5}$ (case 12) respectively.

There was no obvious relation between the grade of hypertensive pulmonary vascular disease and the degree of fall in total pulmonary resistance on breathing of 100 per cent oxygen. Patient 7 with grade 3 lesions showed a substantial fall in total pulmonary resistance on inhalation of 100 per cent oxygen, whereas patients 10 and 12 with grade 4 lesions showed no fall. However, patients 5, 11, and 15, with the severest grades of structural change (grades 5 and 6), showed falls in total pul



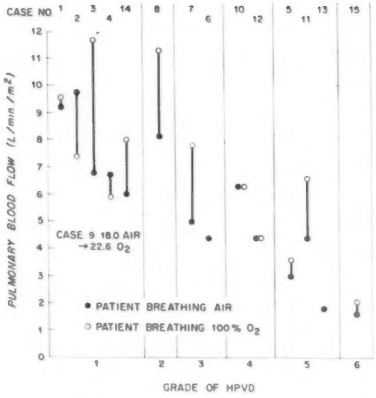


FIG. 3 *Left.* Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and ratio of total pulmonary resistance to total systemic resistance.

FIG. 4 *Right.* Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and pulmonary blood flow.

monary resistance on inhalation of oxygen. In patients 7, 10, and 11, with grade 3, 4, and 5 lesions respectively, the residual resistance after inhalation of oxygen was 400 dynes/sec./cm.$^{-5}$ or less. In patients 5 and 12, with grade 5 and 4 lesions respectively, the total pulmonary resistance was 750 dynes/sec./cm.$^{-5}$ or more on inhalation of 100 per cent oxygen. In patient 15, with grade 6 lesions, the residual total pulmonary resistance was 2,300 dynes/sec./cm.$^{-5}$ after inhalation of oxygen.

These data suggest that the total pulmonary resistance in these cases was compounded of 2 elements, one with a functional, and the other an organic basis. The functional element, defined here as being that part of the total pulmonary resistance removed completely or partially on the inhalation of 100 per cent oxygen, was of major importance in grade 3 lesions and was still present in some patients with grade 4 and 5 lesions. However, in the severest grades, even after administration of 100 per cent oxygen there was still a residual resistance which wholly or in part probably had its basis in organic changes in the pulmonary arteries. By expressing the total pulmonary resistance as a ratio of the systemic vascular resistance and plotting the ratio obtained against the grade of hypertensive pulmonary vascular disease (fig. 3) it is shown that, while breathing air, patients with grade 1 or grade 2 lesions had a ratio of 0.3 or less, whereas those with severest structural changes had a ratio of 0.4 or more in most instances. This ratio is of questionable functional significance, however, in patients with interatrial communication, since the lesser and systemic circulations are not directly connected to a common pumping chamber, as in large ventricular septal defect.

Figure 4 shows the relation between grade of hypertensive pulmonary vascular disease and pulmonary blood flow. In patients with grade 1 lesions the lowest pulmonary flow found was 6.0 L./min./M.^{2}; this is an abnormally high figure, for the highest value in the range of normal is 4.4 L./min./M.^{2}. (See reference 3.) In patients with grade 2, 3 and 4 structural changes, the pulmonary flow was still higher than normal or at the upper limit of normal. In the 3 patients with grade 5 lesions, patient 11 had a pulmonary flow at the upper range of normal, patient 5 had a flow in the normal range, and patient 13 had an abnormally low flow. The patient with grade 6 lesions (case 15) had an abnormally low flow. Figure 4 demonstrates the inverse relationship between pulmonary blood flow and rising grades of vascular change.

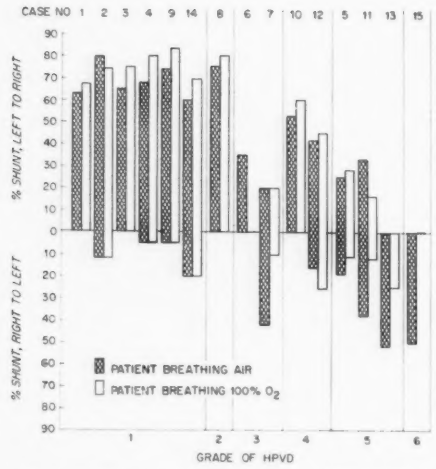

CASE NO 1 2 3 4 9 14 8 6 7 10 12 5 11 13 15
% SHUNT, LEFT TO RIGHT
% SHUNT, RIGHT TO LEFT
PATIENT BREATHING AIR
PATIENT BREATHING 100% O2
GRADE OF HPVD

FIG. 5. Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and percentage of blood shunted in each direction through atrial septal defect.

When the patients inhaled 100 per cent oxygen, there was frequently a rise in the pulmonary blood flow in patients with vascular lesions in the range of grades 1 to 3 (cases 3, 14, 8, and 7). This occurred only exceptionally in patients with a more severe degree of vascular change (case 11), for in grades 4 to 6 there was little or no change in the level of pulmonary flow after inhalation of oxygen (cases 10, 12, 5, and 15).

Figure 5 shows the relation between grade of hypertensive pulmonary vascular disease and percentage of blood shunted in each direction through atrial septal defect. These data show a close relation between the direction and magnitude of shunts through the interatrial communication and the severity of structural changes in the pulmonary arteries in any one case of atrial septal defect.

The patients who had interatrial communication with grade 1 and 2 lesions had large left-to-right shunts and little or no shunting of blood from right to left through the interatrial communication. Of the 2 patients with grade 4 lesions, one (case 10) had a large left-to-right shunt and no reversed shunt, but the other had bidirectional shunts. In the 3 patients with grade 5 lesions (cases 5, 11, and 13) and the patient with grade 6 lesions (case 15), the right-to-left shunt was appreciable. While 2 of these patients (cases 5 and 11) also had demonstrable left-to-right shunts, the others (cases 13 and 15) did not. Patient 7 with grade 3 lesions behaved in an exceptional manner in having not only a left-to-right shunt but also a large right-to-left shunt more commensurate with severer grades of hypertensive pulmonary vascular disease.

On the inhalation of 100 per cent oxygen there was in general a slight increase in the magnitude of the left-to-right shunt and, in the patients with the higher grades of vascular change, a considerable decrease in the magnitude of the reversed shunt (cases 7, 5, 11, and 13). Case 12 was an exception in this respect.

Figure 6 shows the relation between grade of hypertensive pulmonary vascular disease and mean blood pressure in pulmonary artery. There was a close relation between the grade of structural change and the level of the mean blood pressure in the pulmonary artery. In 5 of the 6 patients with grade 1 lesions (cases 1 to 4, and 9) the mean blood pressure was less than 35 mm. Hg. In the sixth (case 14) it was 48 mm. In all the patients with grade 2 to 6 lesions the mean blood pressure in the pulmonary artery exceeded 45 mm. Hg; these form a group that is distinct from those with grade 1 changes, with the exception of case 14. In this respect, case 14 holds an intermediate position and probably represents a transitional stage.

Some patients with severe vascular change maintained a mean pulmonary-artery blood pressure in the region of 50 mm. Hg (cases 5 10, and 11). Others showed a higher mean pulmonary-artery blood pressure commensurate with the anatomic changes in the pulmonary arteries (cases 7, 12, 13, and 15). Little change in this mean blood pressure was noted on the inhalation of 100 per cent oxygen.

Results in Group 2 Cases (Interventricular Communication or Widely Patent Ductus Arteriosus). Figure 7 shows the relation between grade of hypertensive pulmonary vascular disease and age. In contrast to the

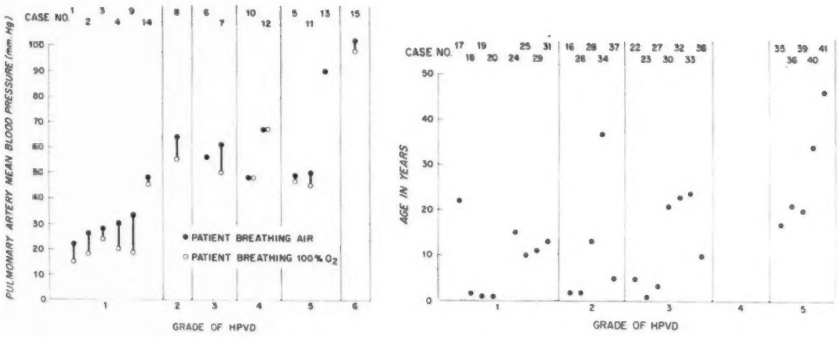


FIG. 6 *Left.* Group 1 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and mean blood pressure in pulmonary artery.

FIG. 7 *Right.* Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and age. No patients in group 2 had grade 4 lesions.

observations with respect to atrial septal defect, there was a close relation between age and the severity of the structural changes in pulmonary hypertension in patients with a large ventricular septal defect or patent ductus arteriosus. Eleven of the 13 patients with cardiac septal defects and grade 1 or grade 2 lesions were 15 years of age or less, whereas 8 of the 12 patients with septal defects and grade 3 to 5 lesions were older than this age. The oldest patient who had grade 1 lesions, except patient 17 who had associated pulmonary stenosis, was 15 years of age (case 24). Patients 22, 23, and 27 had grade 3 lesions by the age of 5 years.

In patients with large interventricular communication or widely patent ductus the systemic pulse pressure is freely propagated into the lesser circulation from birth. Hence the age of the patient is synonymous with the duration of the pulmonary hypertension. Exceptions to this general trend in ventricular septal defect occur when the size of the abnormal communication is below a certain critical level or when there is an associated pulmonary stenosis (case 17), as either the small defect or a stenotic pulmonary valve exerts resistance to the propagation of the systemic pulse pressure and flow into the pulmonary arteries.[5] In illustration of this point, patient 27 had a common atrioventricular canal with free subvalvular communication and with a mean pulmonary-artery blood pressure of 66 mm. Hg and grade 3 pulmonary vascular lesions at the age of only 3½ years. In contrast, patient 17 had only grade 1 lesions by the age of 22 years; this is explained by the presence of an associated mild pulmonary stenosis and a mean pulmonary-artery blood pressure of only 44 mm. Hg.

Figure 8 shows the relation between grade of hypertensive pulmonary vascular disease and total pulmonary resistance. In view of their small size, infants have a high total pulmonary resistance no matter what grade of structural change is present in the pulmonary arteries. If we eliminate some of the patients 2 years of age or younger from figure 8 (cases 26, 20, 18, 19), we find that 11 of the remaining 15 patients with vascular changes included in the range of grade 1 to 3 lesions had a total pulmonary resistance of less than 700 dynes/sec./cm.$^{-5}$. On the other hand, all 4 patients with grade 5 lesions (cases 35, 39, 40, and 41) and 1 patient with grade 3 lesions (case 22) had a total pulmonary resistance exceeding 1,450 dynes/sec./cm.$^{-5}$. Hence, with infants excluded, the total pulmonary vascular resistance in patients with grade 5 lesions or severe grade 3 lesions was roughly double that found in patients with grade 1 to 3 hypertensive pulmonary vascular disease.

On inhalation of 100 per cent oxygen, in-

fants excluded again, there was a substantial fall in the total pulmonary resistance so that it was at or below 650 dynes/sec./cm.$^{-5}$ in all patients with grade 1 to 3 lesions except patient 37. In patient 22, for instance, the total resistance fell from 1,750 to 500 dynes/sec./cm.$^{-5}$. On the other hand, in all 3 patients with grade 5 lesions in whom the total pulmonary resistance had been measured while the patients were breathing air and 100 per cent oxygen respectively, the resistance did not fall below 1,100 dynes/sec./cm.$^{-5}$.

In infants in our series the total pulmonary resistance was high, exceeding 1,100 dynes/sec./cm.$^{-5}$. Similar values for resistance were found in older patients with grade 5 hypertensive pulmonary vascular disease during the inhalation of air and 100 per cent oxygen. In patients with grade 1 and 3 lesions the total pulmonary resistance was usually less than 700 dynes/sec./cm.$^{-5}$.

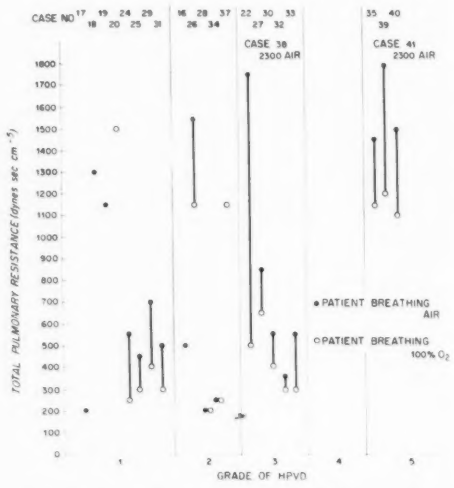


FIG. 8. Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and total pulmonary resistance.

By expressing total pulmonary resistance as a ratio of total systemic resistance and plotting the ratio obtained in each case against the grade of hypertensive pulmonary vascular disease present in that case (fig. 9), a gradual rise is seen in the ratio commensurate with the progression of anatomic changes in the pulmonary arteries. This rise is more apparent if the patients under the age of 2 years are excluded. For the patients on whom sufficient data were obtained to allow calculation of the ratio it is apparent that, with the exceptions of patients 22 and 38, and infants, during the inhalation of air, the ratio was 0.7 or less in those patients with grade 1 to 3 lesions. In patients with grade 5

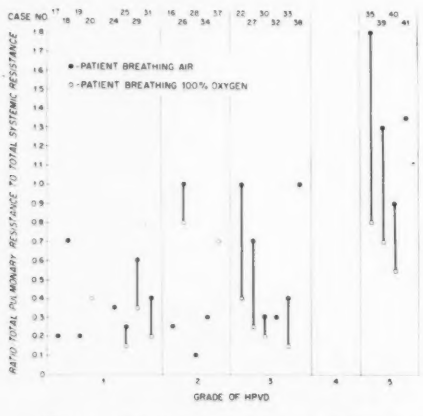

CASE NO
PATIENT BREATHING AIR
PATIENT BREATHING 100% OXYGEN
RATIO TOTAL PULMONARY RESISTANCE TO TOTAL SYSTEMIC RESISTANCE
GRADE OF HPVD

FIG. 9 *Left.* Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and ratio of total pulmonary resistance to total systemic resistance.

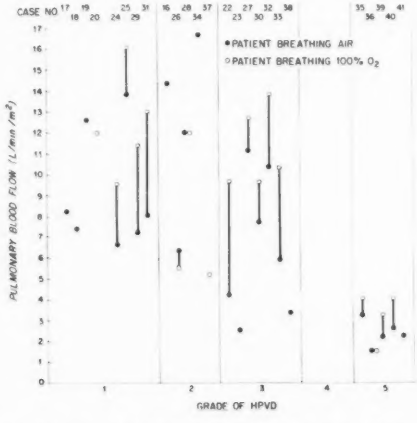


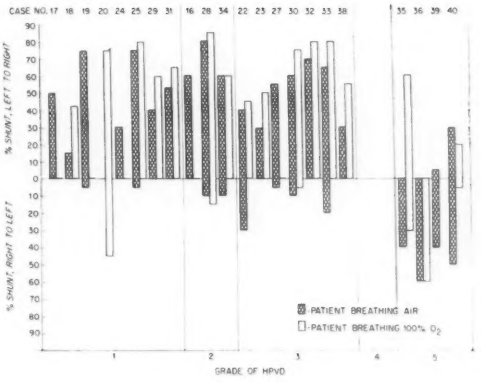
FIG. 10 *Right.* Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and pulmonary blood flow.

lesions the ratio was 0.9 or above; that is, the total pulmonary resistance approached, equalled, or exceeded the total systemic resistance. On the inhalation of 100 per cent oxygen, there was a substantial fall in the ratio of the pulmonary to the systemic resistance, no matter what grade of hypertensive pulmonary vascular disease was present, but it did not fall below 0.5 in the patients with grade 5 lesions.

Figure 10 shows the relation between grade of hypertensive pulmonary vascular disease and pulmonary blood flow. The relation between these 2 factors is the same as that noted in the cases of interatrial communication. All but 3 of the 20 patients with interventricular communication or widely patent ductus arteriosus who had grade 1 to 3 structural changes in their pulmonary arteries had a pulmonary blood flow that exceeded 5 L./min./M.^{2}. In other words, all but 3 (cases 22, 23, and 38) had abnormally high pulmonary flows. The 3 exceptions and 2 of the patients with grade 5 lesions (cases 35 and 40) had pulmonary flows within the normal range of 2.5 to 4.4 L./min./M.^{2}. (See reference 3.) The other 3 patients with grade 5 lesions (cases 36, 39, and 41) had abnormally low pulmonary flows, that is less than 2.5 L./min./M.^{2}. It was in the patients with the more severe forms of grade 3 lesions, where vascular dilatation was associated with vascular obstruction, that the pulmonary flow was at normal and below normal levels.

When the patients breathed 100 per cent oxygen, there was in most instances a rise in the pulmonary blood flow in patients with vascular lesions in the range of grades 1 to 3. In patients with grade 5 hypertensive pulmonary vascular disease there was either little (cases 35, 39, and 40) or no (case 36) increase in pulmonary flow.

Figure 11 shows the relation between grade of hypertensive pulmonary vascular disease and percentage of blood shunted in each direction through septal defect. The patients with structural changes in the pulmonary arteries corresponding to grades 1 to 3 of hypertensive pulmonary vascular disease had


CASE NO. 17 18 19 20 24 25 29 31 16 28 34 22 23 27 30 32 33 38 35 36 39 40
% SHUNT, LEFT TO RIGHT
% SHUNT, RIGHT TO LEFT
PATIENT BREATHING AIR
PATIENT BREATHING 100% O2
GRADE OF HPVD

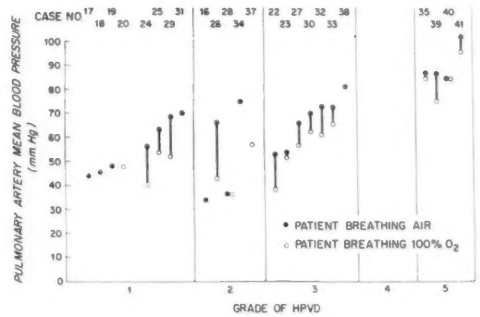

CASE NO. 17 18 19 20 25 24 31 29 16 28 37 34 22 27 30 32 33 38 35 39 40 41
PULMONARY ARTERY MEAN BLOOD PRESSURE (mm Hg)
PATIENT BREATHING AIR
PATIENT BREATHING 100% O2
GRADE OF HPVD

FIG. 11 *Top.* Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and percentage of blood shunted in each direction through ventricular septal defect or patent ductus arteriosus.

FIG. 12 *Bottom.* Group 2 cases. Relation between grade of hypertensive pulmonary vascular disease (HPVD) and mean blood pressure in pulmonary artery.

large left-to-right shunts (not so large, however, as in the patients with atrial septal defect) that increased on the inhalation of 100 per cent oxygen. Some had small right-to-left shunts that disappeared on the inhalation of 100 per cent oxygen. In 2 instances (cases 20 and 28) there was right-to-left shunt that exceeded 10 per cent even when oxygen was breathed; in each instance there was a huge left-to-right shunt that equaled or exceeded 75 per cent.

Although patient 35 (with grade 5 vascular changes) had a large left-to-right shunt on breathing 100 per cent oxygen, and patient 40 had a moderate left-to-right shunt while

TABLE 3.—*Grade of Hypertensive Pulmonary Vascular Disease and Blood Pressures in 3 Cases of Idiopathic Pulmonary Hypertension*

Case no.	Sex, age (years)	HPVD (grade)	Arterial blood pressure in mm. Hg							
			Pulmonary				Radial			
			Mean		Systolic		Mean		Systolic	
			Air	100% O_2	Air	100% O_2	Air	100% O_2	Air	100% O_2
42	F31	3	54	56	77	79	97	92	129	11
43	F30	5	66	59	94	88	90	90	114	1[illegible]
44	M23	5	70	64	99	83	65	89	96	11

breathing either air or oxygen, most patients with the severe grades of structural change had predominantly right-to-left shunts. In case 36, for instance, there was a right-to-left shunt of 60 per cent when the patient was breathing either air or 100 per cent oxygen.

Figure 12 shows the relation between grade of hypertensive pulmonary vascular disease and mean pulmonary-artery blood pressure. A range of 44 to 70 mm. Hg in the mean blood pressure in the pulmonary artery was found in association with grade 1 changes. The development of intimal fibrosis (grade 3 changes) was associated with but slight increase in the mean blood pressure in the pulmonary arteries, for the range found was 53 to 76 mm. Hg. However, in patients with generalized and localized "dilatation (grade 5) lesions," the mean blood pressure in the pulmonary artery was increased to the range of 81 to 102 mm. Hg.

These data suggest that the presence of hypertrophied pulmonary arteries and arterioles is associated with a range of mean pulmonary-artery blood pressure that is maintained but not increased much while progression to severe intimal fibrosis occurs. The stage of obstructive lesions that become associated with vascular dilatation is seemingly associated with a further rise in mean blood pressure in the pulmonary artery.

Results in Three Cases of Idiopathic Pulmonary Hypertension (Tables 3 to 5). Three patients with idiopathic pulmonary hypertension (cases 42 to 44) were studied for purposes of comparison. All 3 patients had severe grades of hypertensive pulmonary vascular disease; patient 42 had grade 3 lesions and patients 43 and 44 had grade 5 lesions. All had severe pulmonary hypertension, which showed little or no change on the inhalation of 100 per cent oxygen (table 3). In all, the total pulmonary resistance was high, exceeding 1,300 dynes/sec./cm.$^{-5}$, and this resistance either remained unchanged (cases 42 and 43) or rose slightly (case 44) on inhalation of oxygen (table 4). The ratio of the pulmonary to the systemic resistance was 0.6 or more in each instance. The pulmonary blood flow was abnormally low in all cases, and fell when the patients breathed 100 per cent oxygen (table 5).

COMMENT

In general, patients[1] with ventricular septal defect who have structural changes in the pulmonary arteries designated as lying in the range of grades 1 to 3 have a moderately elevated pulmonary resistance, pulmonary hypertension, usually an abnormally high pulmonary blood flow, and a predominantly left-to-right intracardiac shunt. Patients with atrial septal defect and the form of grade 1 changes associated with this disease may have normal pulmonary resistance and normal pulmonary-artery blood pressure. Further studies referred to in the foregoing[4] indicate that these patients have pulmonary hypertension that is largely reversible on closure of the septal defect. Application of some of the present data in a previous study[6] suggests that pulmonary arteries showing grade 1, grade 2, and early grade 3 lesions might be considered as forming a "high-resistance high-reserve type of vascular bed." In this type of vascular bed with grade 1 to 3 lesions, the reversible component of the pulmonary hypertension is characteristic.

TABLE 4.—*Grade of Hypertensive Pulmonary Vas- (lar Disease and Vascular Resistance in 3 Cases of I iopathic Pulmonary Hypertension*

ase no.	HPVD (grade)	Total pulmonary resistance*		Ratio of pulmonary to systemic resistance†	
		Air	100% O_2	Air	100% O_2
42	3	1,350	1,400	0.6	0.6
43	5	1,550	1,550	0.7	0.6
44	5	1,300	1,500	0.9	0.7

*To nearest 50 dynes/sec./cm.$^{-5}$
†To nearest 0.05

TABLE 5.—*Grade of Hypertensive Pulmonary Vascular Disease and Pulmonary Blood Flow in 3 Cases of Idiopathic Pulmonary Hypertension*

Case no.	HPVD (grade)	Total pulmonary blood flow (L./min.)		Index of pulmonary blood flow (L./min./M.^{2})	
		Air	100% O_2	Air	100% O_2
42	3	3.2	2.8	2.0	1.7
43	5	3.4	3.0	1.9	1.7
44	5	4.3	3.3	2.1	1.7

The onset of generalized vascular dilata- t on in the late stage of grade 3 lesions with t e subsequent appearance of complex, loca- l zed "dilatation lesions" in grade 4, appears t) represent an important transitional stage (described previously[6] as the "transitional t pe of vascular bed") in the progression of hypertensive pulmonary vascular disease. This stage progresses to that of the grade 5 and 6 lesions, previously termed the high-resistance low-reserve type of vascular bed,[6] in which the pulmonary vasculature appears to become fixed, the pulmonary vascular resistance is grossly elevated, and the pulmonary blood flow is low. This vascular bed is no longer labile, having a predominantly organic basis of structural changes in the pulmonary arteries. The present results show that patients with septal defects of the heart and grade 5 structural changes in the pulmonary arteries have a very high total pulmonary resistance, an abnormally low pulmonary blood flow, and an intracardiac shunt that is predominantly from right to left. Further studies[4] at the time of cardiotomy, which are reported elsewhere, also suggest that patients with grade 5 structural changes in the pulmonary vasculature have irreversible pulmonary hypertension that is on a predominantly organic basis.

Our concept of the progression of vascular occlusion, with associated progressive elevation of pulmonary resistance, diminution of pulmonary blood flow and development of irreversible pulmonary hypertension, depends on the present data, which are derived from isolated cardiac catheterizations in a large number of different patients. It is supported by the finding of a progressive rise in pulmonary vascular resistance in 2 patients with atrial septal defect, each having undergone cardiac catheterization on 3 occasions over a period of 7 years.[7] Furthermore, in regard to ventricular septal defect it is in accord with the description by Dammann and Ferencz[8] of 3 different clinical phases, dependent upon an excessive, a controlled, and a reduced pulmonary blood flow, which together form a characteristic life cycle in patients with malformations of the heart associated with a common ejectile force.

SUMMARY

Studies are presented from 15 cases of atrial septal defect, 19 cases of ventricular septal defect, and 6 cases of patent ductus arteriosus, consisting of results of cardiac catheterization correlated with graded changes in the pulmonary arterial system, obtained by histologic study. From the correlations it is concluded that the grading system is valid as an estimate of those factors which determine the type of resistance to flow through the pulmonary vascular bed, if it is realized that in the very young the normal pulmonary bed has a high resistance.

Grades 1 to 3 indicate a vascular bed which, though it may maintain a moderately high resistance, is labile. Grades 5 and 6 indicate a vascular bed that maintains a high resistance and that is no longer labile. Grade 4 seems to represent a transitional stage between these 2 types of vascular beds.

SUMMARIO IN INTERLINGUA

Es presentate le resultatos de studios in 15 casos de defecto del septo atrial, in 19 casos de

defecto del septo ventricular, e in 6 casos de patente ducto arteriose. Datos obtenite per catheterismo cardiac es correlationate con le grados del alteration in le systema de arterias pulmonar secundo studios histologic. Le correlation permitte le conclusion que le systema de grados es valide in le estimation del factores que determina le typo de resistentia al fluxo in le vasculatura pulmonar, providite que on prende in consideration que le normal vasculatura pulmonar in subjectos de multo basse etates es characterisate per un alte resistentia.

Grados 1, 2, e 3 indica un vasculatura que es labile ben que il es possibile que illo mantene moderatemente alte nivellos de resistentia. Grados 5 e 6 indica un vasculatura que mantene un alte nivello de resistentia sed que ha cessate esser labile. Grado 4 pare representar un stadio de transition inter le 2 typos mentionate de vasculatura.

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BEING TRUE TO ONE'S CONVICTIONS

THOMAS H. HUXLEY

English biologist, 1825-1895

My business is to teach my aspirations to conform themselves to fact, not to try and make facts harmonize with my aspirations.—*Life and Letters of Thomas H. Huxley.* From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon Press, 1952.

Relation between Structural Changes in the Small Pulmonary Arteries and the Immediate Reversibility of Pulmonary Hypertension Following Closure of Ventricular and Atrial Septal Defects

By Donald Heath, M.D., H. Frederic Helmholz, Jr., M.D., Howard B. Burchell, M.D., James W. DuShane, M.D., John W. Kirklin, M.D., and Jesse E. Edwards, M.D.

The relative importance of organic changes and vasoconstrictive influences in the production of increased pulmonary vascular resistance in congenital heart disease is problematic. With use of a grading system previously described, a study was made of the relation between each of the grades of hypertensive pulmonary vascular disease associated with ventricular or atrial septal defects and the change of pulmonary artery blood pressure immediately following closure of the abnormal communications. The immediate reversibility of the pulmonary hypertension varies inversely with the severity of the structural changes.

IN PATIENTS in whom there is a large communication between the left ventricle or aorta on the one hand and the lesser circulation on the other, the pulmonary arteries are subjected from birth to a systolic blood pressure of systemic magnitude. In patients with a large interatrial communication, pulmonary hypertension is classically acquired in later life. Progressive occlusive changes occur in the small pulmonary arteries in the presence of pulmonary hypertension which diminish their lumina and exaggerate the pulmonary vascular resistance, thus initiating a vicious circle. Although it is preferable to proceed with repair of septal defects before the occlusive vascular changes have occurred, many candidates for operation have structural changes in the pulmonary vessels. It becomes important to know whether there is a stage of hypertensive pulmonary vascular disease at which the pulmonary artery pressure fails to fall at the time the defect is closed. The present communication reports an investigation into the relation between histologic changes in the small pulmonary arteries and the immediate change of pulmonary artery blood pressure following closure of defects in the ventricular or atrial septa.

From the Mayo Foundation and the Mayo Clinic, Rochester, Minn. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

This investigation was supported in part by research grant no. 3531 from the National Heart Institute, National Institutes of Health, U.S. Public Health Service.

Method and Material

Thirty-two patients were studied. All had congenital septal defects of the heart associated with pulmonary arterial hypertension, the severity of which ranged from slight to severe in different cases studied. All the patients died for various reasons after surgical repair of the septal defects. The operations were performed over a period of 2 years. For the purposes of this investigation the patients were considered in 2 groups.

Group 1 (table 1) was composed of 26 patients who had large interventricular communications and hence were considered to have had pulmonary arterial systolic hypertension from birth. Eight of these cases (cases 18, 22, 26, 28, 30, 32, 33, and 34) were used in a previous study[1] along with other cases relating the grade of hypertensive pulmonary vascular disease to physiologic data including blood pressure, flow and resistance in the pulmonary artery. In these 8 instances the same case numbers have been retained to allow easy cross reference between the 2 papers. As the highest case number in the previous paper was case 44, the new cases included in this study are

TABLE 1.—*Blood Pressures in the Lesser and Systemic Circulations and the Grade of Hypertensive Pulmonary Vascular Disease in the Cases in Group 1*

HPVD* (grade)	Case no.	Age (yrs.)	Sex	Before closure of defect			After closure of defect			Anatomic diagnosis§
				A, F, or LV†	RV or PT‡	Ratio	A, F, or LV†	RV or PT‡	Ratio	
1	18	1½	M	60/15 LV†	56/10	0.93	50/12 LV	10/0	0.20	VSD+CTR+ASD
	45	2	M	68/32	47/-2	0.69	70/28	17/0	0.24	VSD
	46	2	F	80/54	65/2	0.81	74/29	27/0	0.36	AVC
	47	2	M	115/58 F	56/4	0.49	113/49 F	46/5	0.41	VSD
2	48	6	F	95/60	78/11	0.82	80/44	25/7	0.31	VSD
	34	37	F	80/60 F	74/42 PT	0.92	97/49 F	38/14 PT	0.39	VSD+ASD
	49	1	M	90/43 F	50/18 PT	0.55	118/50	34/10 PT	0.29	VSD
	28	13	M	73/9 LV†	65/5	0.89	63/7 LV	30/3	0.48	AVC
	50	3	M	94/40	75/17 PT	0.80	77/24	35/15 PT	0.45	ASD+CTB
	51	8	M	80/42 F	34/1	0.43	102/62 F	39/6	0.38	VSD+MI
3	33	24	M	109/44 F	81/8	0.74	183/25 F	33/7	0.18	VSD
	52	5	F	80/38	65/4	0.81	80/45	25/0	0.31	VSD+MI
	22	5	F	70/42	75/5	1.07	64/27	29/5	0.45	VSD+MI
	26	2	M	82/26	58/24 PT	0.71	92/34	33/15 PT	0.36	VSD+PDA
	53	2	M	65/38	54/8	0.83	118/86	54/5	0.46	VSD+X
	32	23	F	114/82 F	90/25 PT	0.79	95/42 F	45/24 PT	0.47	VSD
	54	14	F	91/48	82/8	0.90	65/38	44/5	0.68	VSD
	55	5	F	110/53	56/5	0.51	118/63	38/7	0.32	VSD+MI
	56	11	F	78/59 F	87/7	1.12	99/49 F	49/9	0.50	AVC
	57	8	M	96/48 F	48/2	0.50	110/48 F	23/6	0.21	VSD
4	30	21	F	66/0 LV†	65/0	0.99	127/0	55/0	0.43	VSD
	58	15	F	137/63 F	86/5	0.63	101/70 F	65/9 66/47 PT	0.64	VSD+PDA
	59	4	M	97/60	101/60 PT	1.04	123/89	89/48 PT	0.72	VSD
	60	10	F	109/72 F	92/15	0.84	89/36 F	58/10	0.65	AVC+CA
5	61	7	F	104/47	65/43 PT	0.63	90/43	60/36 PT	0.66	VSD+MI
	62	6	F	72/36 F	90/46 PT	1.25	66/44	89/0 PT	1.35	VSD

*Hypertensive pulmonary vascular disease.

†Blood pressures from the aorta unless femoral artery (F) or left ventricle (LV) is indicated.

‡Blood pressures from the right ventricle unless pulmonary trunk (PT) is indicated.

§VSD, ventricular septal defect; CTR, corrected transposition of great vessels; ASD, atrial septal defect; AVC, common atrioventricular canal with subvalvular communication; CTB, cor triloculare biatriatum without pulmonary stenosis; MI, mitral incompetence; PDA, patent ductus arteriosus; X, origin of both great vessels from right ventricle; CA, common atrium.

designated by case numbers beginning at case 45 and extending to case 66.

Among the patients in group 1, 11 had only a ventricular septal defect. Ten others had a large ventricular septal defect associated with other congenital defects of the heart. These were an atrial septal defect in 1 case, a patent ductus arteriosus in 2, origin of both great arteries from the right ventricle in 1, mitral incompetence in 5, and corrected transposition of the great vessels with atrial septal defect in 1. In 4 of the 5 remaining cases the interventricular communication was part of a persistent atrioventricular canal. In 1 of these there was an associated common atrium. The final case was one of single ventricle with atrial septal defect.

Group 2 (table 2) was composed of 6 patients who had interatrial communications. In 5 of these patients pulmonary hypertension was present and was considered to have been acquired after a period of high pulmonary blood flow. Two of these patients had been included as cases 5 and 11 in the study previously referred to[1] and are similarly designated here. Two of the 6 (cases 5 and 65) had a simple atrial septal defect. In 2 others (cases 11 and 64) partially anomalous pulmonary venous connection was associated with an atrial septal defect. In case 64 an anomalous superior vena cava and situs inversus were present. In 2 cases (cases 63 and 66) a common atrioventricular canal was present without subvalvular communication, and these cases therefore are classi-

TABLE 2.—*Blood Pressures in the Lesser and Systemic Circulations and the Grade of Hypertensive Pulmonary Vascular Disease in the Cases in Group 2*

PVD* (grade)	Case no.	Age (yrs.)	Sex	Before closure of defect A or F†	RV or PT‡	Ratio	After closure of defect A or F†	RV or PT‡	Ratio	Anatomic diagnosis§
	63	1	F	62/36 F	50/6	0.81	63/27	34/3	0.54	AVC
1	64	3	F	106/50	34/0 PT	0.32	68/23	27/21 PT	0.40	ASD+AnSVc+
	65	35	F	78/52	71/48 PT	0.91	89/51	71/47 PT	0.80	AnPVs+SI
2	66	5	F	92/55	70/34 PT	0.76	75/43	36/16 PT	0.48	ASD AVC+COARC (mild)
3	5	32	F	118/60	85/36 PT	0.72	97/0	76/44 PT	0.78	ASD
	11	46	F	99/48	53/23 PT	0.53	101/48	62/26 PT	0.61	ASD+AnPVs

AnSVc, anomalous superior vena cava.
AnPVs, partial anomalous venous connection.
SI, situs inversus.
COARC, coaretation of aorta.
* † ‡ §, see footnote to table 1.

fied with the cases of interatrial communication; in case 66 mild coaretation of the aorta was present also.

SURGICAL PROCEDURE

Repair of the congenital defects was carried out with the aid of extracorporeal circulation, polyvinyl sponge (Ivalon) being sutured into place to close them completely. In case 50, with cor triloculare biatriatum, a complete ventricular septum was created in this manner, and the associated atrial septal defect was closed. Defects of the atrial septum were closed with use of the atrial well, the Ivalon sponge being placed in such a manner as to allow anomalous pulmonary veins to drain within the newly created limits of the left atrium. In each of the 32 cases included in this study blood pressures were measured in the lesser and systemic circulations at the time of thoracotomy before and after closure of the septal defect. The site for obtaining systemic pressure was the left ventricle, the aorta or the femoral artery, and the site for obtaining blood pressures in the lesser circulation was either the right ventricle or the pulmonary trunk. In any one case the same sites were used to measure the blood pressure in the 2 circulations before and after closure of the defect. The ratios obtained by dividing the systolic pressure in the lesser circulation (P_{sp}) by the systolic pressure in the systemic circulation (P_{ss}), from measurements made before and after closure of the defects, are used as an index of the acute change in the pulmonary hypertension following repair of the defect.

The necropsy carried out in each case afforded anatomic proof of the diagnoses recorded in tables 1 and 2 and of complete closure of the various defects present. Cases in which the septal defect was not closed completely were not included in this study. Portions of lung, usually from the upper and lower lobes of each lung, were embedded in paraffin and sections of these blocks were stained by Verhoeff's and van Gieson's stains. The grade of hypertensive pulmonary vascular disease in each instance was assessed according to criteria described in detail in a previous paper.[2] These data are included also in tables 1 and 2 to allow an examination of the relation between the degree of immediate reversibility of the pulmonary hypertension in each case and the nature of the structural changes in the small pulmonary arteries. The previous paper[2] should be consulted for a detailed explanation of the grade numbers, but in general it may be said that the higher the grade number the more severe and extensive were changes in the pulmonary arteries and arterioles.

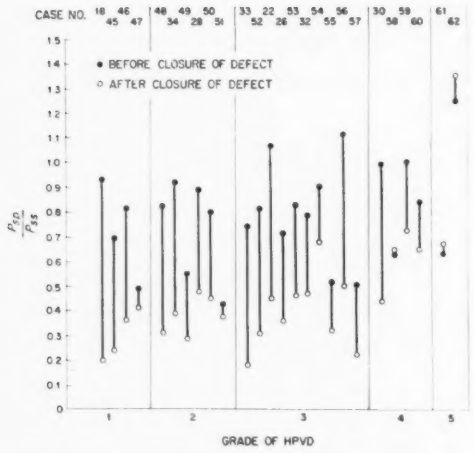
CASE NO. 18 46 45 47 | 48 49 50 34 28 51 | 33 22 53 54 56 52 26 32 55 57 | 30 59 58 60 | 61 62
• BEFORE CLOSURE OF DEFECT
○ AFTER CLOSURE OF DEFECT
$\frac{P_{SD}}{P_{SS}}$
GRADE OF HPVD

FIG. 1. The relation between the grade of hypertensive pulmonary vascular disease (HPVD) and the ratio of the systolic blood pressure in the lesser circulation to that in the systemic circulation (P_{sp}/P_{ss}), before and after closure of a ventricular septal defect in 26 patients.

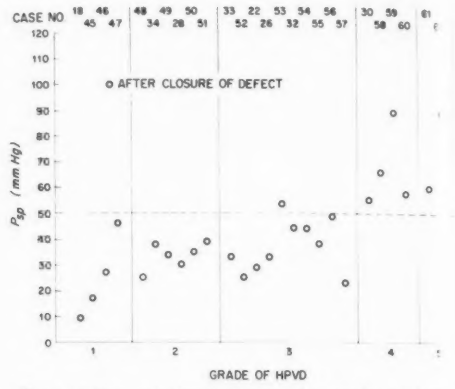

FIG. 2. The relation between the grade of hypertensive pulmonary vascular disease (HPVD) and the residual systolic blood pressure in the lesser circulation (P_{sp}) following closure of a ventricular septal defect in 26 patients.

RESULTS

The age, sex, anatomic diagnosis, grade of hypertensive pulmonary vascular disease, and hemodynamic data in each case in group 1 are shown in table 1 and in group 2 in table 2. The hemodynamic data given are the blood pressures in the systemic and lesser circulations. The ratio of the systolic blood pressure in the lesser circulation to that in the systemic circulation (P_{sp}/P_{ss}) in each case at the time of thoracotomy both before and after closure of the septal defect is also shown.

For group 1 the relation between the grade of hypertensive pulmonary vascular disease and the ratio P_{sp}/P_{ss}, before and immediately after closure of the ventricular septal defect and correction of any associated defect, is plotted in figure 1. This ratio was plotted for the cases of free communication between the ventricles but not for the cases of interatrial communication. The magnitude of the fall in this ratio after closure of the ventricular septal defect is attributable to that proportion of the pulmonary hypertension which is related to increased flow and possibly other features such as vasoconstriction. The residual systolic hypertension in the lesser circulation after closure of the ventricular septal defect is, on the other hand, probably determined by the proportion of the pulmonary hypertension which has its basis in organic changes in the pulmonary arteries and possibly in residual vasoconstriction. The relation between the grade of hypertensive pulmonary vascular disease and the systolic blood pressure in the lesser circulation (P_{sp}) following closure of the ventricular septal defect is plotted in figure 2. Hence information as to the presence and extent of immediate reversibility of pulmonary hypertension associated with each histologic grade of structural change in the pulmonary arteries is provided in figure 1, and information as to the presence and extent, immediately after repair, of residual pulmonary hypertension associated with each grade is provided in figure 2.

In interatrial communications the pulse pressure of the left ventricle is not propagated into the lesser circulation and for this reason we have not included a graph showing the ratio P_{sp}/P_{ss} in the cases of group 2. Instead, for this type of malformation in figure 3, the grade of hypertensive pulmonary vascular disease is plotted against the systolic blood pressure in the lesser circulation (P_{sp} before and immediately after closure of the

d ect. It is considered that this provides i rmation as to what proportion of the pul- m nary hypertension was acutely reversible i each case.

entricular Septal Defect (Group 1). In e ry case of hypertensive pulmonary vascu- la disease of grades 1 to 3 inclusive in which th P_{sp}/P_{ss} ratio was equal to or greater than 0. before closure, the ratio showed a sub- st ntial decrease on closure of the defect (fig. 1 In 2 cases (cases 47 and 51) of hyperten- si e pulmonary vascular disease of grades 1 a d 2 respectively, the ratio, which was al- re dy less than 0.5 before closure of the defect, fe l only slightly. In every case of grades 1 to 3 the residual systolic pressure in the les- se circulation, after repair of the defect, was less than 55 mm. Hg and in all but 1 (case 53) it was less than 50 mm. Hg. These re- sults were interpreted as indicating that in the presence of only medial hypertrophy in the pulmonary arteries and arterioles (grade 1 changes[2]) or of associated intimal prolifera- tion of a cellular (grade 2) or fibrous nature (grade 3) the pulmonary hypertension was associated with a high pulmonary flow and was largely reversible as a result, principally, of elimination of the large left-to-right shunt.

In 3 of the 4 cases (cases 30, 59, and 60) with grade 4 lesions in the pulmonary arteries, there was a considerable fall in the P_{sp}/P_{ss} ratio but in the fourth (case 58) there was no significant change. In spite of the fall in the ratio in 3 of the cases in this subgroup all 4 had a residual systolic blood pressure in the lesser circulation exceeding 55 mm. Hg.

In the 2 cases of grade 5 hypertensive pul- monary vascular disease (cases 61 and 62) no fall, but in fact a small rise, in the P_{sp}/P_{ss} ratio occurred. In both, the residual s stolic blood pressure in the lesser circula- t on exceeded 55 mm. Hg.

These results were interpreted as indicating t at in the presence of generalized vascular d latation in association with multiple foci of f brous occlusion and localized complex "dila- t tion lesions," defined as occurring in grades 4 and 5 hypertensive vascular disease,[2] the p lmonary hypertension is largely on an organic basis, not associated with a high pul- monary flow, and is irreversible, at least im- mediately after closure of the cardiac defect.

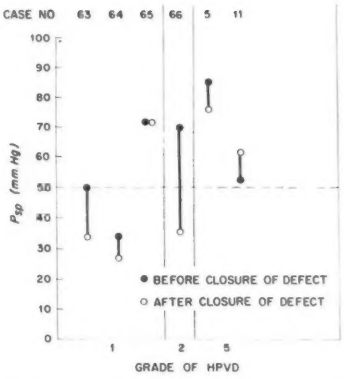

FIG. 3. The relation between the grade of hypertensive pulmonary vascular disease (HPVD) and the systolic blood pressure in the lesser circulation (P_{sp}) before and after closure of an atrial septal defect in 6 patients.

Interatrial Communication (Group 2). The pulmonary arteries showed structural changes of grade 1 or 2 in 4 cases. The systolic blood pressure in the lesser circulation which was initially 50 mm. Hg or more in 3 of these cases decreased substantially in 2 cases (cases 63 and 66) to about 35 mm. Hg after repair of the atrial septal defect. There was a smaller fall in the systolic blood pressure in case 64, but the original level was only 34 mm. Hg. The 2 cases of grade 5 lesions showed, in 1 instance (case 11), a slight rise in the systolic blood pressure in the lesser circulation and, in the other (case 5), a slight fall after surgical closure of the interatrial communication. In both, the final systolic blood pressure exceeded 60 mm. Hg.

In the exceptional case (case 65) there was no change in the blood pressure in the pulmonary artery although only grade 1 structural changes were present.

COMMENT

The relative importance of organic changes and vasoconstrictive influences in the production of increased pulmonary vascular resist-

ance is problematic. With the development of adequate surgical methods for the correction of congenital cardiac defects the basis of the pulmonary hypertension in any given patient with organic vascular changes or abnormally high pulmonary blood flow remains the central problem in the treatment of congenital septal defects, including patent ductus arteriosus. Biopsy of the lung has on occasion been used to detect the presence of organic vascular changes and to evaluate their significance so as to assess the likelihood of a fall in blood pressure in the pulmonary arteries after the planned closure of the defect which predisposes to the pulmonary hypertension.

Dammann and Ferencz,[3] in a study of hypertensive pulmonary vascular disease complicating congenital cardiac anomalies, considered that it was "perhaps too late to operate" when narrowing of the pulmonary arteries by progressive medial hypertrophy and intimal fibrosis had caused pulmonary resistance to exceed systemic resistance and so had produced a right-to-left shunt. Their uncertainty is mirrored in the phraseology they used and indeed they stated, "we do not know when, in the course of the disease, pulmonary vascular changes become so severe that operation is no longer indicated and may even be contraindicated." Heath and Whitaker,[4] considering the problem in relation to patent ductus arteriosus, expressed similar uncertainty that progressive intimal changes "are perhaps irreversible and explain why the pulmonary artery blood pressure may fail to fall or may even rise after ligation of the ductus in some patients with pulmonary hypertension." The above view considers that the vascular changes influence the characteristics of the shunt.

The results of the present investigation confirm that the pulmonary hypertension associated with large ventricular septal defects is compounded of (1) a reversible component, indicated by a fall in the P_{sp}/P_{ss} ratio after closure of the defect, which is produced by high pulmonary blood flow, by transmission of the systemic blood pressure to the pulmonary vessels, and possibly by constrictive influences, and (2) a component not immediately reversible, at least, due to organic vascular changes. The latter is indicated by residual elevation in the systolic blood pressure in the lesser circulation after closure of the defect when the pulmonary blood flow is considered not to be elevated. In grades 1 to 3, the earlier stages of hypertensive pulmonary vascular disease, in which there is medial hypertrophy alone or associated with intimal proliferation of a cellular or fibrous nature, the hypertension was completely or largely acutely reversible after closure of the defect (tables 1 and 2, figs. 1 to 3). In grades 4 and 5, stages of hypertensive pulmonary vascular disease usually seen in adults with pulmonary hypertension of many years standing, the hypertension was largely unchanged immediately after closure of the defect (tables 1 and 2, figs. 1 to 3). Here the basis for the pulmonary hypertension seems related more to organic vascular changes than to other factors such as increased pulmonary blood flow or vasoconstriction. The results show, however, that even in some examples of changes graded 4, functional as well as organic causes of pulmonary hypertension are still operative.

A significant feature in the results of this investigation is that the functional component was still important in all the patients who had grade 3 lesions with intimal fibrosis and even in some with grade 4 lesions when "plexiform lesions" are present in addition to widespread severe intimal fibrosis (fig. 1). It is significant, however, that the systolic blood pressure in the lesser circulation usually fell to less than 50 mm. Hg in the patients with grade 3 changes in the pulmonary arteries but never did so in patients with grade 4 changes. These observations make it plain that in the face of occlusive lesions the onset of dilatation in the pulmonary vasculature, an essential feature of grade 4 hypertensive pulmonary vascular disease, rather than simply intimal fibrosis characterizing grade 3, is an important transition from the stage when the pulmonary artery blood pressure falls immediately after closure of the defect to the stage when it does not.

The practical importance of these data is obvious. When biopsy of the lung discloses

intimal fibrosis associated with medial hypertrophy with no evidence of dilatation in the small pulmonary arteries, blood pressure in the pulmonary arteries will probably fall after closure of a ventricular septal defect. Only when the pulmonary vasculature has entered the stage of chronic fibrotic dilatation (grade 5) with the development of the characteristic "dilatation lesions" can one predict that almost certainly there will be residual pulmonary hypertension immediately after repair or that the blood pressure in the lesser circulation may even rise after closure of a ventricular septal defect. Some of the patients with grade 4 hypertensive pulmonary vascular disease with early "dilatation lesions" responded to closure of the defect by some lowering of the pulmonary hypertension, but all had residual pulmonary hypertension immediately after repair (cases 30 and 58 to 60).

The results demonstrated that, under the conditions of this investigation, there is in a given case a close relation between structural alterations in the pulmonary arteries and the change in the pressure immediately after closure of the cardiac defect. It is recognized that the present results were obtained when the patients were under anesthesia during thoracotomy. While patients with pulmonary vascular changes classified as grades 1 to 3 had reversible pulmonary hypertension under such conditions, it is obviously impossible to predict whether the blood pressure in the pulmonary arteries would have remained at normal levels under the influences of exercise and the stresses of everyday life. Even in some patients having a favorable fall in the pulmonary blood pressure some residual abnormality of the pulmonary arteries might result in pulmonary hypertension on exposure of the patient to the conditions of exercise with increased pulmonary blood flow. Likewise it remains to be seen whether some patients with residual pulmonary hypertension immediately after repair may show regression of this in the months after operation.

Difficulties in the Assessment of Pulmonary Biopsies. Since the progression from grade 3 to grade 4 marks the transition from a largely reversible to an irreversible pulmonary hypertension, it is desirable to recognize grades 3 and 4 with assurance. Although this is possible in most cases, there must be a minority of cases in which the anatomic changes lie between those of grades 3 and 4 proper. Assessment of biopsies of the lung from such patients would be difficult, and predictions as to the functional consequences of closure of defects would be unreliable.

On occasion, a biopsy from a lung that subsequently proves to be the seat of severe pulmonary vascular disease will show only vascular dilatation without intimal fibrosis. This paradoxical situation is readily explained by the focal nature of intimal fibrosis in cases of congenital heart disease with pulmonary hypertension. The focal character of intimal changes must always be borne in mind when pulmonary biopsy is being assessed to avoid the error of giving too low a grade number, with all its implications.

Summary

The histologic grade of hypertensive pulmonary vascular disease, based on the criteria described in a previous communication,[2] was related to the immediate change in pulmonary artery blood pressure following closure of a defect in the ventricular or atrial septum in each of 32 patients with congenital heart disease. Twenty-six had a ventricular septal defect, and 6 had an interatrial communication.

In 23 of the 24 cases of medial hypertrophy alone (grade 1) or associated with intimal proliferation of a cellular (grade 2) or fibrous (grade 3) nature in the pulmonary arteries the pulmonary hypertension was largely immediately reversible, the residual systolic blood pressure in the lesser circulation being less than 50 mm. Hg.

In all 4 of the cases of generalized dilatation of pulmonary arteries and localized complex "dilatation lesions" associated with multiple occlusive fibrotic lesions (grade 5) the pulmonary hypertension was unchanged immediately after repair of the defect and the residual systolic blood pressures in the lesser circulation exceeded 50 mm. Hg.

In 3 of the 4 cases of early dilatation of pul-

monary arteries (grade 4) the pulmonary hypertension was partially reversible and in the fourth it was irreversible. In all 4 cases in this subgroup, there was a residual systolic blood pressure in the lesser circulation exceeding 50 mm. Hg.

These data suggest that pulmonary vascular resistance and associated hypertension are composed of functional and organic components, the latter becoming increasingly important as the changes of hypertensive pulmonary vascular disease become more severe. Difficulties in the assessment of pulmonary biopsies are discussed.

SUMMARIO IN INTERLINGUA

Le grado histologic de hypertensive morbo pulmono-vascular—secundo le criterios describite in un previe communication[2]—esseva relationate al alteration immediate in le pression de sanguine pulmono-arterial post clausion de un defecto in le septo ventricular o atrial in 32 patientes con congenite morbo cardiac. Vinti-sex del patientes habeva un defecto del septo ventricular. Le altere 6 habeva un communication interartrial. In 23 del 24 casos de hypertrophia medial del arterias pulmonar —sin alteration intimal (grado 1) o associate con proliferation intimal de natura cellular (grado 2) o de natura fibrose (grado 3)—le hypertension esseva in grande mesura immediatemente reversibile, e le residue pression systolic in le circulation minor esseva minus que 50 mm de Hg.

Inomne le 4 casos de dilatation generalisate del arterias pulmonar e de localisate complexe "lesiones de dilatation" associate con multiple occlusive lesiones fibrotic (grado 5), le hypertension pulmonar non se alterava immediatemente post le reparo del defecto le residue pression systolic in le circulation minor remaneva plus que 50 mm de Hg.

In 3 del 4 casos de dilatation precoce del arterias pulmonar (grado 4), le hypertension pulmonar esseva partialmente reversibile. In le quarte de iste casos, le reversibilitate esseva complete. In omne le 4 casos de iste subgruppo, le residue pression systolic in le circulation minor esseva plus que 50 mm de Hg.

Iste datos pare indicar que le resistentia pulmono-vascular e le associate hypertension consiste de componentes functional e organic. Le componentes organic deveni de plus in plus importante in tanto que le hypertensive morbo pulmono-vascular deveni plus sever.

Difficultates in le evalutation de biopsias pulmonar es discutite.

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The P Wave, P-R Interval, and Q-T Ratio of the Normal Orthogonal Electrocardiogram

By HUBERT V. PIPBERGER, M.D., AND HERBERT L. TANENBAUM, M.D.

The shortcomings of electrocardiographic time measurements from single leads have been noted before. With the use of simultaneously recorded corrected, orthogonal leads it is possible to evaluate better the time phase relationships of the electrocardiogram. The present study involves a statistical analysis of measurements of the P-wave duration, P-R interval, P-R segment, Q-T duration, and Q-T ratio of a group of 133 normal subjects.

ELECTRIC signals generated from the heart are more properly defined in magnitude and direction by an orthogonal 3 lead system with constancy in lead direction and strength.[1-5] The spatial heart vectors are projected on the 3 perpendicular axes of such a Cartesian coordinate system, and are readily available for analysis. With the advent of corrected orthogonal lead systems[1-4] it appeared appropriate to reevaluate the time-phase relationships of the electrocardiogram in simultaneously recorded tracings of the 3 orthogonal leads. Such an analysis should come very close to the determination of the true beginning and end of electric events as they take place in the heart, as far as these can be ascertained from the body surface.

In previous studies by Blackburn and Simonson[6] and from this laboratory[7] it was found that the QRS duration differs markedly from commonly accepted, normal standards when simultaneously recorded tracings of orthogonal leads are analyzed. It seemed apparent, therefore, that other intervals used in electrocardiographic interpretations should also be reinvestigated in the same fashion. White and associates[8] and Lepeschkin and Surawicz[9] have discussed the shortcomings of electrocardiographic time measurements from single leads. More accurate time-phase determinations may yield clinical information hitherto not available.

The present study involves a statistical analysis of measurements of the P-wave duration, P-R interval, P-R segment, corrected Q-T interval, and Q-T ratio in a group of 133 normal subjects. Schmitt's SVEC III leads[1] were used. A high degree of constancy in lead strength and direction of this system has been demonstrated previously in torso models[1, 10] and in man.[5]

MATERIAL AND METHODS

Tracings were taken from 133 subjects who were admitted to Georgetown University Hospital and the Veterans Administration Hospital, Washington, D.C., for reasons other than heart disease. A complete clinical evaluation including a standard 12 lead electrocardiogram did not reveal any signs or symptoms of past or present cardiac pathology. The age and sex distribution of these patients are shown in table 1. The mean heart rate of these cases was 77 ± 11 per minute, with a range from 50 to 99.

Recordings from 101 subjects were taken on 5 inch photographic paper with a film speed of 118 mm. per second. The remainder of the tracings were recorded on 35 mm. film with a film speed of 28 mm. per second. A photographic enlarger was used for the analysis of these records with an 8 fold magnification, resulting in an apparent film speed for reading of 224 mm. per second. Such large record sizes and film speeds facilitated the measurements of the data. The electronic characteristics of the high-fidelity recording apparatus have been described previously.[5]

The baseline was established between 2 points on the T-P interval of 2 consecutive complexes.

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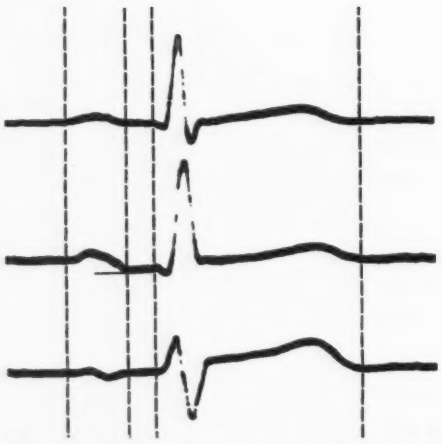


FIG. 1. Simultaneously recorded tracings of leads X (*top*), Y (*middle*) and Z (*bottom*). The total P-wave duration, P-R interval, P-R segment, and Q-T duration are indicated by the *broken lines*. Note the discrepancies between the different leads for the onset and end of deflections. The retrograde prolongation of the P-R segment in lead Y shows the method used for the determination of the end of the P waves.

These points were taken just prior to the onset of the P wave. All measurements were made from the lower edge of the tracings.

The *total P wave duration* was determined as follows: The beginning of the P wave was taken at the point of its earliest departure from the baseline in any one of the 3 leads (fig. 1). Because the P-R segment in most cases does not coincide with the preestablished baseline, a different method had to be used for the determination of the end of the P wave. The P-R segment baseline was extrapolated backward, as illustrated in lead Y of figure 1. The intersection of this line with the preceding P wave wherever it occurred latest in the 3 leads was marked as the end for the measurement of the total P-wave duration. The individual P waves from each lead were measured separately as well.

The *amplitude of the P wave* was measured between the preestablished baseline (T-P) and the highest point of each P deflection. In some instances, most notably in lead Z, the P amplitude could not be measured accurately because of the biphasic or flat characteristic of the deflections.

The *P-R interval* was measured from the earliest P deflection to the earliest QRS deflection of the 3 leads. The *P-R segment* was taken as the difference between the P-R interval and the total P-wave duration.

The *Q-T duration* was measured from the earliest QRS deflection to the end of the latest T deflection of the leads. The *corrected Q-T duration* or Q-Tc was calculated by dividing the actual Q-T duration by the square root of the preceding R-R interval. The mean result for Q-Tc was used as a constant K for the calculation of the Q-T ratio, according to the formula[11]

$$\frac{\text{Q-T duration}}{K\ \sqrt{\text{R-R}}}$$

RESULTS

Mean results, standard deviations, standard errors, and ranges of the measured parameters are presented in table 2.

The vertical lead Y was the most reliable of the 3 for the determination of the total P-wave duration. In 35 per cent of the cases, however, P_Y was found shorter than the total P (table 2, 6).

A normal Gaussian distribution was found for the total P-wave duration, P-R interval, and P-R segment. The distribution curve for the P/P-R segment ratio, however, appeared drawn out toward the higher values (fig. 2). The 8 cases exceeding the confidence limits of the mean plus 2 standard deviations were singled out for further analysis. P-wave durations and P-R intervals of these patients were found inside the established confidence limits. The large values for the P/P-R segment ratio could therefore be attributed solely to short P-R segments.

Results were further analyzed by correlating age and heart rate with the total P-wave duration, P-R interval, and P-R segment, respectively. No significant correlations were found between any of these parameters. However, several interesting factors were noted. Beyond the age of 60, the total P-wave duration was greater than 0.095 second in all cases

TABLE 1.—*Age and Sex Distribution of the Subjects Studied*

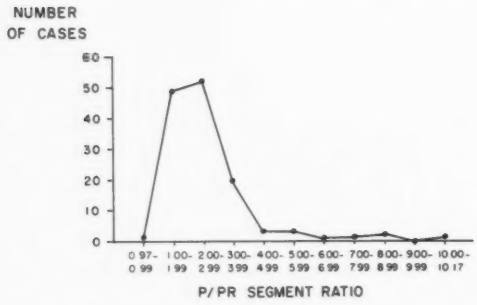
Age group	Number of subjects	
	♂	♀
21—30	20	5
31—40	28	12
41—50	20	14
51—60	11	11
61—70	8	1
71—83	1	2

TABLE 2.—*Mean Results and Ranges for the Normal Orthogonal Electrocardiogram*

1. Total P-wave duration	0.102 ± 0.013 sec., SE* 0.001 sec. Range: 0.068 — 0.141 sec. (133)
2. P-wave duration	0.079 ± 0.019 sec., SE 0.002 sec. Range: 0.038 — 0.127 sec.
Lead X	(129)
Lead Y	0.096 ± 0.018 sec., SE 0.002 sec. Range: 0.025 — 0.131 sec.
	(132)
Lead Z	0.072 ± 0.019 sec., SE 0.002 sec. Range: 0.025 — 0.110 sec.
	(130)
3. P-wave amplitude (positive deflections)	
Lead X	0.07 ± 0.02 mV, SE 0.002 mV Range: 0.03 — 0.15 mV
	(127)
Lead Y	0.11 ± 0.04 mV, SE 0.004 mV Range: 0.03 — 0.26 mV
	(131)
Lead Z	0.06 ± 0.03 mV, SE 0.003 mV Range: 0.02 — 0.12 mV
	(84)
4. Number of cases with biphasic P waves	
Lead X	0
Lead Y	2
Lead Z	55
purely negative P waves	
Lead X	0
Lead Y	0
Lead Z	2
5. Amplitude of negative P-wave deflections	
Lead Y	0.03 mV (1)
Lead Z	0.05 ± 0.02 mV, SE 0.006 mV Range: 0.02 — 0.08 mV
	(10)
6. Percentage of cases with total P-wave duration equal to P-wave duration	
Lead X	24
Lead Y	65
Lead Z	10
Total P-wave duration longer than any of the 3 leads	17
7. P-R interval	0.135 ± 0.024 sec., SE 0.002 sec. Range: 0.101 — 0.211 sec. (133)
8. P-R segment	0.047 ± 0.017 sec., SE 0.001 sec. Range: 0.010 — 0.093 sec. (133)
9. Ratio between total P-wave duration and P-R segment	2.56 ± 1.42, SE 0.12 Range: 0.97 — 10.17 (133)
10. Q-T duration	0.367 ± 0.028 sec., SE 0.002 sec. Range: 0.283 — 0.444 sec. (133)
11. Q-T_c (corrected Q-T duration)	0.41 ± 0.027, SE 0.002 Range: 0.34 — 0.52 (133)
12. Q-T ratio (calculated on the basis of the mean Q-T_c of 0.41)	1.0 ± 0.065, SE 0.006 Range: 0.82 — 1.26 (133)

Measurements that appeared unreliable for technical reasons were not included in this tabulation. The number of subjects for each measured item is given in parenthesis. For the methods of measurements see text.

*SE = standard error.



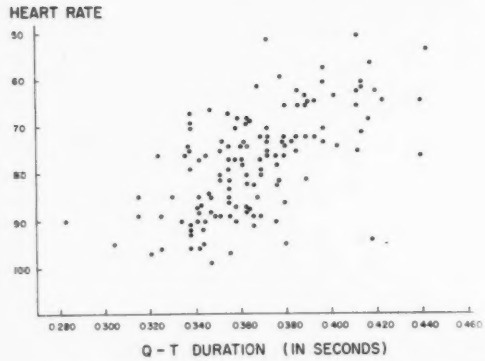


FIG. 2 *Top.* Distribution curve of the P/P-R segment ratio. Note the large extension of the total range toward high values.

FIG. 3 *Bottom.* Scattergram of the Q-T duration (*abscissa*) and heart rate (*ordinate*). A very low correlation coefficient of −0.17 was found between the 2 parameters.

except one, and the P-R interval greater than 0.135 second. In general, smaller P-wave durations and P-R intervals were noted at higher heart rates; however, deviations from this rule were frequent. P-R segments shorter than 0.025 second were found only with heart rates greater than 75 per minute.

The mean corrected Q-T duration (Q-Tc) was also calculated for each sex. It was found to be 0.407 ± 0.025 in males and 0.426 ± 0.026 in females. The difference was not significant ($p > 0.05$).

The actual Q-T duration was correlated with the heart rate. Although an apparent correlation was noted on a scattergram (fig. 3), the correlation coefficient was found to be low (−0.17). The marked scatter noted in relating the Q-T interval to heart rate, especially in individuals over 50 years of age, has been commented on by Klakeg et al.[12]

Discussion

P-Wave Duration. The total P-wave duration as determined from the simultaneously recorded orthogonal leads was considerably larger than the generally accepted normal standards of the conventional electrocardiogram.[13] Caceres and Kelser,[14] who analyzed recently standard electrocardiographic leads of a smaller group of normal persons, have also noted larger limits for the normal range of P duration. Some of their results exceeded those of the present study. The discrepancies may be partially due to differences in the recording technic. Enlarged tracings from a direct-writing electrocardiograph were analyzed. The thickness of the tracings relative to oscilloscopic records may conceivably add to the length of measured waves.

No single lead was sufficiently reliable to indicate the total P-wave duration. With lead Y taken as the most reliable of the 3 leads, the total P duration would have been missed in 35 per cent of the present series. This finding indicates the need of the use of multichannel recorders in electrocardiography for greater accuracy in time-phase analysis.[6-9]

P-R Interval. Stewart and Manning[15] reported a higher mean value for the P-R interval in conventional electrocardiograms than found in the present study. This, in part, can be explained by the difference in time for the onset of the QRS deflection recorded in different leads.[6-9] A lead with an isoelectric interval at the beginning of QRS may point to an apparent P-R interval prolongation. Likewise, discrepancies in the apparent onset of the P and QRS deflections in different leads can account for the larger range of P-R intervals noted.

P-R Segment. The range for this parameter was relatively large. This limits the diagnostic usefulness of this criterion.

Total P/P-R Segment Ratio. With the recent attention directed to the use of the ratio between P-wave duration and P-R segment as a means of evaluating left, right, or combined atrial enlargement,[16] it was of interest to

s udy this ratio from the available data. As i noted on table 2, 9, the range of this ratio v as found to vary from 0.97 to 10.17. This v riability would also limit the diagnostic s gnificance of this ratio insofar as values have t be extremely large or small to exceed the n rmal range.

Q-Tc and Q-T Ratio. The mean corrected (T duration (Q-Tc) of 0.41 and the Q-T r tio did not differ markedly from results ob- t ined by other investigators.[13] It was sur- p ising to note that a correlation between the (T duration and heart rate resulted in a v ry low correlation coefficient, —0.17. Such a result, however, does not necessarily rule out a relationship between the 2 parameters as n ore than one factor can conceivably influ- e ce the Q-T duration. Mainland[17] has pointed out again recently that the significance of such statistical correlations can be obscured by additional factors that are not under test in the correlation.

Summary and Conclusions

Measurements of the P wave, P-R interval, and Q-T ratio were made in a group of 133 normal subjects from simultaneously recorded orthogonal electrocardiograms (Schmitt's SVEC III system). Most results differed from generally accepted normal limits. The discrepancies were essentially due to the recorded differences in the onset and termination of the electric cardiac events as measured from separately recorded leads. There was no single lead that reliably indicated the true duration of these events. These findings indicate a need for the use of simultaneously recorded leads for greater accuracy of time measurements from the electrocardiogram.

Acknowledgment

The authors gratefully acknowledge the very helpful suggestions and criticisms of Dr. Edward D. Freis. They are very much indebted to Mrs. Hanna A. Pipberger for her technical assistance and the statistical analysis.

Summario in Interlingua

Esseva effectuate mesurationes del unda P, e el intervallo P-R, e del proportion Q/T in le simultaneemente registrate electrocardiogrammas (systema SVEC III de Schmitt) de un gruppo de 133 subjectos normal. Le majoritate del resultatos differeva ab le generalmente acceptate limites normal. Le discrepantias resultava essentialmente ab le registrate differentias in le declaration e termination del evenimentos electro-cardiac in comparation con mesurationes super le base de separatemente registrate derivationes. Nulle del derivationes presentava per se un indication fidel del ver duration de ille evenimentos. Le constatationes del presente studio indica le necessitate del uso de derivationes a registration simultanee pro augmentar le accuratia del mesurationes in le electrocardiogramma.

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Wood, H. F., Stollerman, G. H., Feinstein, A. R., Hirschfeld, I., Rusoff, J. H., Taranta, A., Haas, R. C., and Epstein, J. A.: A Controlled Study of Three Methods of Prophylaxis against Streptococcal Infection in a Population of Rheumatic Children. I. Streptoccal Infections and Recurrences of Acute Rheumatic Fever in the First Two Years of the Study. New England J. Med. **257**: 394 (Aug. 29), 1957.

The present report considers the incidence of streptococcal infections and recurrences of rheumatic fever observed during the first 2 years of a large-scale, carefully controlled 5-year study of children with unequivocal histories of rheumatic fever maintained on prophylaxis against streptococcal infection. The clinical material consisted of 405 children, all of whom had had a definite attack of rheumatic fever within the preceding 28-month period. The prophylactic regimens used were as follows: a single daily oral 1-Gm. dose of sulfadiazine, a single oral dose of 200,000 units of penicillin half an hour before breakfast, and an intramuscular injection of 1,000,000 units of benzathine penicillin G every 4 weeks. The data obtained indicated that 1,200,000 units of benzathine penicillin G, given intramuscularly every 4 weeks, was more effective in preventing both streptococcal infections and rheumatic recurrences than either of the other 2 methods of prophylaxis. Probable reasons for this superiority are that the benzathine penicillin is injected, thus giving assurance that prophylaxis is received, and that each monthly injection also provides a probable eradicating dose of penicillin for group A streptococci, a property not present in the dose schedule used for the other 2 agents.

Sagall

PANEL DISCUSSION

Guest Editor: HERBERT POLLACK, M.D.

Present Status of Lipid Metabolism and Atherosclerosis

The Panel was comprised of the following members: HERBERT POLLACK, *New York, N.Y.*, MODERATOR; ROBERT E. OLSON, *Pittsburgh, Pa.*; OGLESBY PAUL, *Chicago, Ill.*; and HERMAN E. HILLEBOE, *Albany, N.Y.*

The Panel Discussion was conducted at the Thirtieth Scientific Sessions of the American Heart Association held at the Sherman Hotel, Chicago, Illinois, on Sunday, October 27, 1957.

MODERATOR POLLACK: This panel was designed to try to answer some of the questions that are being raised today in connection with the subject of the etiology of atherosclerosis. Cardiologists have been so concerned with the diagnosis and treatment of clinical cardiologic disorders up to fairly recently that they did not have time to occupy themselves with the etiology of one of the principal causes of myocardial disease, that is atherosclerosis.

The reopening of this question of the etiology of atherosclerosis has been rather bewildering because it brings up new terminologies and technics foreign to the electronic principles that have engaged many of the clinical cardiologists. They have been forced to listen to such terminology as poly-unsaturated fatty acids, iodine numbers, beta sitosterol, and many other names that are new in the cardiologic literature.

Another new aspect of this subject has been the epidemiologic one. Here again the cardiologist as a rule has not kept pace with the development of epidemiologic technics, the study of the community as a whole rather than the patient as an individual.

To start the panel today, I should like to ask Dr. Herman E. Hilleboe, Commissioner of Health of the State of New York, to open the discussion on the etiology of atherosclerotic heart disease.

DR. HERMAN E. HILLEBOE: I should like to express a few views on the epidemiology of atherosclerosis, particularly some of its terminal effects in the heart. In coronary artery disease, for example, we are dealing with a disease entity that appears to have multiple factors in its causation as well as in its manifestations. We feel that by observing its natural history among people under varying environmental conditions and mode of life, we may be able to unmask some of the hidden secrets. This we call the epidemiologic method of study. It is no different from that used in the study of the infectious diseases in the past except that we are dealing here with diseases that are of unknown etiology, and we are therefore at a distinct disadvantage.

We must use indirect methods of study. Consequently it is necessary for us to talk about associations and degrees of associations and not about cause and effect. Certainly our work with tuberculosis seemed complex, even though we knew the cause was the tubercle bacillus and we could classify pulmonary lesions as minimal, moderate, and far advanced. We cannot do this clinically with atherosclerosis, which manifests itself in the heart and brain and in the peripheral circulation. I think that we need not know the cause of diseases in order to do something about them. If we can learn enough about their epidemiologic characteristics to detect their occurrence early and to prevent their progression then public health workers and private practitioners can proceed collectively to do something about them.

The biggest criticism that we would make of some of the work going on—and I hope that this is considered as constructive criticism—is that we are dealing with diseases difficult to define. In the literature and in the work that is done, we find that defining coronary artery disease itself or the manifestations of atherosclerosis are in quite a confused state. We find that in the living individual, because of the difficulty of determining the incubation period of coronary artery disease, we are at a loss to study its natural history. We know, too, that postmortem studies present difficulties in classification.

In addition, as we view some of the studies throughout the world on the natural history of atherosclerosis we find great difficulty in bridging the gaps that occur. Specifically in coronary artery disease we think first of the diet itself, the components of the diet, particularly fat, the fat content of the blood, the fat composition of the arteries in which we are particularly interested, and the terminal episode.

It is very easy to relate the diet to several constituents in the blood. We cannot by inference jump from the relationship between these 2 things to the relationship between the constituents in the blood and the cause of impairment and death. Our greatest gap occurs at this point.

As epidemiologists we start out initially by studying the principal factors. For example, in coronary atherosclerosis we are interested in any relationships that there might be between the available food, as for example the fat in the diet, and death from various types of coronary artery disease or associated heart conditions. It is easy to select a half dozen countries and to show a linear relationship between the available fat in the dietary of the countries and the mortality from arteriosclerotic heart disease. But if we look more extensively into the available food and the mortality from heart disease, we at once learn that the picture is not so simple as it might appear.

The first comment that I would make as an epidemiologist is that we must not alter the facts that should be considered before constructing a hypothesis that we will try to prove.

It has been shown by a study of the data from as many as 22 countries that if we review the figures concerning the available food supplies and the mortality, the apparent association observed when applied to a limited number of countries is greatly reduced; also that the basic data are subject to considerable limitations. This caution applies both to the components of the diet in the different countries and to the mortality, especially to the classifications of causes of death. In addition the presumed association is not specific for fats in the diet nor for diseases of the heart. For instance, the association of mortality from heart disease with diet is stronger when the correlation is with animal protein. There is a negative association that we find for both animal protein and fat with mortality from noncardiac disease. It is not enough simply to rack up a series of positive instances where those things that we would like to show are available. We need to think of the negative instances and to explain them at the same time.

Purely on a statistical basis we can conclude from the available data, poor as they may be, that the suggested associations between national death rates from heart disease and the percentage of dietary fat available for consumption cannot at the present time be accepted as statistically or epidemiologically valid. From this conclusion we can proceed to the additional studies in the chain effect, i.e., where inferences are drawn from the constituents of the diet, particularly fat, to the constituents of the blood, to the constituents of the vessels of the arteries, to the effect that we will call coronary artery disease or some other type of disease such as cerebrovascular disease.

Finally, in looking over the work that is going on in this field of atherosclerosis and its effect on the morbidity and the mortality of the population, we see certain areas where more work needs to be done. Certainly a tremendous amount has been done on the relation between elements in the diet and some ele

ments in the blood. But in the effect of the diet on the coagulation factors in the blood, there may well be a relationship of greater importance than that of the mechanical basis of fat in the blood and fat in the vessel walls themselves.

There are other factors to be considered, i.e., the relationship to occupation and to mental stress.

In conclusion, as epidemiologists concerned with this complicated study, we are perhaps the critics who stand back and look at the disease as a whole as it affects the population. Those of you who study groups of individuals must give us good data and we will attempt to put together the array of facts in an orderly fashion for mutual interpretations. Until such time as we can find reasonable justification for affecting the population as a whole, I think we must keep many of our activities purely on an experimental level.

MODERATOR POLLACK: Each of the panelists will be asked to give a brief discussion of one aspect of this problem and then questions from the floor will be invited. When honest men disagree, as the late John Peter said, then obviously there was something in the conditions under which they were working that differed. It is up to us to find out just why these conditions appear to be the same but are basically different.

As the next part of this topic, Dr. Robert Olson, of Pittsburgh, will discuss the physiologic and biochemical aspects of blood lipid and the dietary relationship involved.

DR. ROBERT OLSON: The idea that atherosclerosis results from a disorder in lipid metabolism probably dates from the very early observations of German pathologists. They noted that the lipoidal material that they could isolate from the atheroma resembled in general the composition of the serum. These observations were followed by the classic experiments that showed that by feeding cholesterol to rabbits experimental atherosclerosis could be induced. Since this time the preoccupation of the biochemists with the idea that atherosclerosis is a disorder of lipid metabolism has increased. The search for truth has opened up in a marvelous way many avenues of research, including the establishment of new technics which I think are going to revolutionize the biochemists' concept of fat metabolism, such as column chromatography, gas phase chromatography, and many other technics that have attracted a number of workers in this field.

I think it would be amiss to be so preoccupied in the field of lipid metabolism to believe that it is the only factor involved in the pathogenicity of atherosclerosis. The weight of my remarks will be directed toward the idea that we must not lose sight of many other factors involved in the pathogenesis of this disease, some of them certainly completely nonlipoidal and foreign to the area of fat metabolism.

Taking a lead from Dr. Hilleboe's discussion of the epidemiology, I will consider the triangle which the epidemiologist deals with in the general analysis of infectious disease. He relates by a triangle the host, the environment, and the agent. The problem with atherosclerosis is that the agent is not easy to find. It may not exist as a single entity, but certainly we can say that circumstances which lead to the formation of atheroma arise by interaction between host and environment. The agent is endogenous. To complicate the picture further we can add those factors that seem to bear some relationship to the progress of atherosclerosis in the host: heredity, race, age, sex, endocrine glands, and even the psyche. The environmental factors that have been implicated in one way or another include diet, not only the fat content but other nutrients that have an effect on the fat metabolism, certain drugs among which we might include beta sitosterol, exercise, occupation, and possibly even culture and climate.

At the upper end of the triangle we can segregate some local factors and some humoral factors arising in the host as a result of interaction and environment. We might segregate factors such as serum lipids, lipoprotein-clearing factors, and coagulability of the blood, and even have local factors that affect the response of the artery. They include

hemodynamic factors, dealing with pressure and turbulence, metabolic factors dealing with the arterial tissue itself, with its structural composition and any trauma that it undergoes.

To highlight this multiple etiology further I relate diet, which is so widely discussed today, to clinical events that can be measured by the clinician or the epidemiologist. Between these 2 determinants there lies a tenuous route of association possibly because I am going from diet, to serum lipids, to the process of atherogenesis, and then to the clinical event. We know that this line of association is not a direct line, and the length and strength of the connections cannot be precisely defined at the present time for a population or for an individual.

We have to recognize that the effect of diet —and the caloric balance, the protein intake, the fat intake, the carbohydrate intake, and possibly even the mineral and the vitamin intake—may have some influence not only upon serum lipids but upon other events in this chain, and we have to recognize other factors operating at each level to produce this disease.

In discussing this problem I refer to the multiple factors even at the site of interaction between beta lipoproteins and serum. You will agree that there may also be a determinant in the process of atheromatosis in the artery itself.

One can see possible sites of breakdown in this system at the present time. Changes in the intima due to thrombus formation may be the first. Much emphasis has been placed upon changes in the elastic membrane, and even here we must invoke the concept of multiple etiology.

The relationship of serum cholesterol to clinical events, mostly of myocardial infarctions, has been analyzed in 5 populations of individuals studied by the Public Health Service over the past several years. There is a wide distribution of cholesterol values, from 150 mg. per cent up to very high values.

We cannot with this evidence make a 1:1 relation between serum fat and clinical disease. It is interesting, however, that many of the subjects with infarcts seem to cluster above the midpoint, between the 50 and the 75 percentile of the serum cholesterol distribution curve; this distribution confirms the fact that the serum profile is one determinant of atherosclerosis but its quantitative significance in a given individual, or even a given population, in my opinion has yet to be evaluated.

I present what is a reasonable summary of our concepts of fat metabolism at the present time relating to 3 organs, the gut as the site of absorption, the liver which serves as the site of transformation, and the depots which serve as the site of storage. The fat that is absorbed by the gut passes to the liver and the other tissue, and the liver transforms this chyle in large amounts to lipoproteins, etc.

Further, we know that in certain cases, such as diabetic acidosis and in starvation and in certain pituitary disorders, the depots can mobilize a great amount of lipid, for example, chylomicrons, and transform it to beta lipoproteins, and the response is often an increasing output of beta lipoproteins. I would like to call your attention to the liver, possibly a central organ in mediating the response of depots of fatty acids mobilized in various ways; also the liver may have an important influence in transforming dietary modifications of the lipoprotein profile.

In conclusion, I would say that at the present time the physiologist should look upon— I think is compelled to look upon— atherosclerosis as a disease of multiple etiology in which disorders of lipid metabolism may play a role. Secondly, beta lipoproteins appear to be a determinant in the process of atherogenesis but their quantitative significance is yet to be precisely evaluated. Third, dietary manipulations can alter the serum cholesterol and lipoprotein configuration. The extent to which this happens in individual cases and in individual populations in the presence of varying components of diet other than fat is still a subject for investigation.

Finally, I would make the plea that every physician taking care of middle-aged patients

consider himself a clinical investigator in this particular period when data are needed about the relationship of the diet and of the lipid levels and of the natural history of atherosclerosis, to define the problem further so that some reasonable position at the public health level can be taken.

MODERATOR POLLACK: Dr. Oglesby Paul will now discuss the clinical aspects of this problem.

DR. OGLESBY PAUL: Dr. Olson has brought the clinician into the story, and what can one say in ten minutes about the clinical phases of coronary heart disease that we don't already know? I doubt if we can say anything new, but we can perhaps emphasize certain points that may be helpful.

The multiple-factor theory is helpful for the clinician to keep in mind. We all have patients who are fat—overweight—who go on until the mid-eighties and never get into trouble. We have lazy patients and patients with high serum cholesterol who likewise do not get into trouble. If we think in terms of a disease process in which different weightings of these factors may be important, we have an approach that helps us to understand some of the clinical variables we see in our offices and in hospital and clinic practice.

I hope that this multiple-factor theory does not exclude the possibility that the control of 1 or 2 critical factors may permit the control of the disease as such. If it were necessary to control each and every item Dr. Olson listed, this, indeed, might be a hopeless problem.

As clinicians, I think it is important that we recognize that we are not making a diagnosis of atherosclerosis as such except under rare instances. When we make a diagnosis of atherosclerosis with involvement of the coronary bed, what we are really diagnosing, as you know, is the complication of atherosclerosis. It is only when infarct or ischemia occurs that we are able to say with any certainty that an individual has coronary heart disease. But it isn't even this simple, because we have, as the coronary disease progresses, a similar development of collateral circulation. When a patient has symptomatology due to coronary disease, it represents the inadequacy of both the collateral circulation and the coronary circulation with which he was endowed.

The variable course of this disease is one of the problems that is sometimes forgotten, and in too small a group of patients, particularly patients who are followed without adequate controls, I think that we get utterly and totally lost. This is particularly true of small groups that are treated by physicians in the office and in clinic and hospital practice, where the relatively good outlook over a short period of time would make one consider that one is getting satisfactory results.

Just to remind you how variable is this disease with its remissions and exacerbations, I will present very simply the course of a few patients illustrating some aspects of this fact. First is an individual going from 1944 with a course that is now actually associated with less angina than he had for a period of many years. Next is another individual who 21 years ago had his first infarct, which is well documented. He had another infarct, a ventricular aneurysm, and advanced angina decubitus; and he is now free of angina. Next is an individual who has gone along with essentially the same amount of symptomatology for a period of 12 years.

We are deluding ourselves if we think of this disease as being either a malignant disease with a standard predictable progression or that it is a disease with a standard stable course. It is neither, and it will take a good many cases, followed over a good many years, by each of us, before we can get satisfactory data regarding the course of the disease and the effect obtained by any agent.

Finally, I would like to remind this audience that all of us who see patients are having difficulties with the publicity that attends the subject of fat in the diet. If the American public has a weakness, it certainly has a weakness for going into a panic at certain times. You will remember the mock invasion from Mars that struck New York some years ago when everybody headed for the hills. I think that maybe Sputnik has had a similar effect on the American public. The medical litera-

ture and the drug literature relating to the subject of fats and cholesterol, and the papers you have heard here today, all serve to create a wave of public interest that creates a problem in the hospital, in the clinic, and in the office. It requires patience and conservatism to withstand the onslaught of patients, press, radio, and television, and to withstand the temptation to make a dogmatic statement and to give treatment with a certainty not justified.

MODERATOR POLLACK: The panel will now entertain and invite questions from the floor for further discussion.

While we are waiting for some of the people in the audience to gather their thoughts, Dr. Hilleboe, I would like to ask you if you would care to comment briefly as to whether or not we are running into an increasing epidemic of coronary heart disease.

DR. HILLEBOE: This question must take into consideration several factors. First of all, we have an aging population and, as you know, with an aging population we have more disease of various types, including atherosclerosis and its various manifestations. So corrections must be made for the change in the age and sex distribution of our population.

Secondly, we must recall that in 1949 there was a change in the nomenclature of the disease, and that if we attempt to make studies of long-term trends of the disease going from a period of time at the turn of the twentieth century to the present we must have an adjustment at 1949, because we called coronary artery disease one thing before that time and another thing after that time.

Thirdly, we know that within the short space of the last 10 years there has been quite a change in the accuracy and the completeness of the diagnosis of coronary heart disease. I happen to serve on one of the advisory committees to the National Office of Old Age and Survivors' Insurance, and twice a year we review some of the samples of diagnoses received from physicians. Some of them have been made by older physicians, middle-aged physicians, and recent graduates, and certainly the types of conditions that are called coronary heart disease are legion, because we go all the way from simple angina to the classical picture with changes in the electrocardiogram and changes in the x-ray, with the history and physical findings and other laboratory findings.

So these are the factors that we must consider when we judge whether or not there has been an increase in coronary artery disease. I would say offhand that the increase has been more apparent than real. The extent to which it has increased is modified by the factors that I have mentioned. Properly considered they show that there has been not quite as proportionately great an increase as one would suspect from a cursory examination of recent figures.

MODERATOR POLLACK: Dr. Paul, you were talking about the distribution of atherosclerotic lesions in the body. Would you mind commenting on why the pulmonary tree is free from atherosclerosis?

DR. PAUL: Of course, atherosclerotic lesions can occur in the pulmonary circulation where pulmonary hypertension exists. Under normal circumstances, however, the pressure in the pulmonary artery is about one quarter or less than that in the peripheral circulation and the mean pressure is similarly lower. So we have normally a difference in lateral pressure on the vessel wall in the two circulations, which is at least a partial explanation of this freedom from atherosclerosis in the pulmonary vascular bed. When the pulmonary artery has been subjected to increased pressure, atherosclerotic plaques may develop.

MODERATOR POLLACK: Then you are still of the old school that believes possibly hypertension has little to do with atherosclerosis?

DR. PAUL: Yes. I think the studies done recently by the Public Health Service in Framingham, for example, demonstrate that hypertension is one of the factors that may predispose to atherosclerosis involving the coronary tree, and their data, which were collected over a good many years and under careful circumstances, would indicate not that hypertension per se is necessarily a critical factor but that hypertension in association

with overweight and hypercholesteremia is a factor.

MODERATOR POLLACK: In all of this discussion the word vitamins has not been introduced. I cannot think of any discussion on nutrition that does not involve vitamins. Dr. Olson, do you want to discuss the role of vitamin B_6 or pyridoxine in atherosclerosis?

DR. OLSON: There is some good evidence on the subject and some additional speculation. We know from the work of several laboratories that vitamin B_6 deficiency in the primate—in the monkey—can cause atheromatous lesions in the large vessels and in the coronary arteries of that species. These are characterized more by intimal proliferation than by fatty infiltration or deposits in the intima. In fact, in the B_6 deficient monkey the serum lipids are quite low.

We also know that niacin at high levels does affect the serum cholesterol level. I am sure that the mechanism of this effect is familiar to pharmacologists. It is not nutritional in the sense of the usual intake of this vitamin, but it provides another interesting problem.

MODERATOR POLLACK: All of which raises the question, Dr. Paul, what would your recommendation be with respect to some of these preparations on the market now that are mixtures of the poly-unsaturated fatty acids and pyridoxine, vitamin B_6, etc.?

DR. PAUL: I can settle this very easily; as to vitamin B_6, no. As to the other preparations that you mentioned I am not aware of any solid evidence that any of them added to the diet affects the course of coronary atherosclerosis, and until I personally have some more solid evidence, I would be glad to have some other people, as has been mentioned in the 2 preceding papers, follow groups of patients and see how they come out. I think if each of us in this room give a little of this and a little of that, we are not going to learn anything and I am sure that we are just going to deceive the patient into thinking that we are really doing something for him. I do not believe, therefore, that the dietary supplements, the vitamin supplements, the fatty-acid supplements are going, in a general, free distribution fashion, to give us any useful information and I would prefer that they not be employed except under rather rigid and carefully controlled experimental conditions.

MODERATOR POLLACK: I would like to ask a loaded question of the panel and give each one a chance to answer it. That is, what is your advice today to patients with respect to the fat content of their diets? Do you tell patients to eat low fat diets, do you disregard fat all told, or just how do you approach it?

DR. OLSON: I would like to answer that loaded question in a circuitous way by commenting upon the attention of physicians to diet therapy in general. Many of our colleagues think that diet therapy is something measurable, that you put the patient on a diet and then he is going to be better, and in many instances, the diet, no matter what it is, is not studied from the point of view of the effect upon the patient's lipid pattern, general well-being, incidence of angina, or future course.

I think that physicians in general have to accept clinical nutrition as a very important part of their armamentarium, a specialty of medicine really, and really learn themselves something about the problems of diet prescription and diet adherence.

With that preface, I would say that in my mind the problem again is centered at the individual patient-doctor level at the present time.

In our own clinic we are studying several combinations of diet therapy for patients with clinical evidence of atherosclerosis. My own feeling is that the evidence today suggests that the unsaturated fats provide the best avenue of diet therapy for controlling serum cholesterol. In our clinic we are studying the effect of incorporating unsaturated fat in various proportions with saturated fat at a level of about 40 per cent of the calories in diets that will maintain weight in these patients. But, as I say, this problem is unsettled and I think it is premature to say without further evidence of this kind, which we all should participate in, that this course or that course is

the preferred one for prevention of further progress of this disease.

DR. HILLEBOE: We attempt to approach something of this kind on the basis of the best advice we can get from the experts. By the experts we mean the cardiologists, the laboratory people, the epidemiologists—anyone who can contribute to basic knowledge for the control of a chronic disease. Our problem amounts to working with the state and the local medical societies in putting out health information that people understand and with which we have some hope of succeeding in affecting the population.

When we use these two means in an attempt to get people to cut down the fat in their diets we fail in both of them. In the first place we do not yet have sufficient reason to state from the available scientific literature and the studies that have been made, including our own studies, that if you cut down the fat in the diet over a period of time you will reduce the amount of morbidity and mortality from heart disease, cerebrovascular disease, peripheral artery disease, or the various manifestations of atherosclerosis. If we cannot give good reasons, it does not seem to us wise to go forward.

Secondly, it is exceedingly difficult to get people to cut down their weight just on general principles, particularly if they are well. It is one of the most difficult problems in medicine. A patient may diet, and reduce 20 pounds, but most of the time he has those 20 pounds back very soon, unless the individual has an incentive related to himself or to his family. This is a task on which a great deal of effort is expended and very little success is obtained.

So we would take this position. At the present time we would rather concentrate our efforts with organized medicine and volunteer health agencies, particularly the Heart Association, to get people who are overweight to cut down their weight by proper reduction of total calories. There is good evidence that by doing so general well-being is improved and that mortality from various types of heart disease is affected. This we can do and this I think is intelligent. In the present state of our knowledge if we attempted to do otherwise and it turned out later that our advice had been bad what would people expect of us in the future? I think that we need to be conservative in this particular respect.

DR. PAUL: I think that there are essentially 3 groups of people that you are interested in here. For people in good health, if they are overweight, you are on solid ground in suggesting a diet that will reduce their total weight and that will reduce their total calories and that will include necessarily a reduction in their fat intake.

The second group is those patients who have a very bad family history of coronary disease and have perhaps also hypercholesteremia. Should we do nothing for those individuals? Should we have them ride a bicycle around the block 10 times a day? Should we have them see a psychiatrist? Or should we give them a diet? If they are not overweight and they still have this bad family history and hypercholesteremia, I myself give those people a try at a moderately low fat diet.

Third, if you have a patient with coronary disease either with angina or myocardial infarction do you do anything for him? I believe that there is some evidence, which many of us have confirmed clinically, that the patient who eats a high fat meal tends to have angina after it. There are some good data indicating that this may occur, and certainly I have had patients of my own in whom a high fatty meal has resulted in the appearance of angina. For that reason as well as for the control of weight itself, I think that caution in the amount of fat taken in is desirable. It do not recommend that these people go on a strict, low fat diet.

MODERATOR POLLACK: One question has been brought up from the audience. Can essential steroid functions be harmed by effective reduction of cholesterol?

DR. OLSON: It has been shown that cholesterol can be a precursor for a number of steroid hormones, but the percentage of body cholesterol diverted for hormone synthesis is minimal. We know also that these hormones

can be synthesized de novo from acetate, so that the body pool of cholesterol over any dietary regime would produce hypocholesteremia would not in any way interfere with the synthesis of the steroid hormones.

MODERATOR POLLACK: Are there any other questions from the audience?

DR. SIDNEY STRAUSS: In this whole meeting I have heard only one etiology for coronary disease: atherosclerosis. I want to call your attention to the fact that there may be an arteriosclerotic lesion of the coronary artery with hardening and gradual narrowing until even without a thrombotic formation you get an infarct. What about the fats in that type of coronary disease? I think some of these anginas which Dr. Paul showed were probably arteriosclerotic lesions.

MODERATOR POLLACK: Dr. Strauss' question serves to re-emphasize the extreme difficulty involved in this whole question. As has been pointed out by several of the speakers, the question of diagnosis is almost impossible at times. The principal part of the disease starts long before it is diagnosed. The progress of the condition goes on without being detected. Differentiation, as now introduced between atherosclerosis, arteriosclerosis, and so forth, is still wide open and I do not know the answer to it. Would anyone on the panel care to pick up Dr. Strauss' question?

DR. PAUL: I think that when we use the term coronary atherosclerosis we are using it interchangeably with the general term used in the standard nomenclature, arteriosclerotic heart disease and that is what we are referring to.

DR. HILLEBOE: The chairman has presented a question to me that really covers a lot of territory. Before I answer it I want to know whether you want to hear it. I will read the question and if you want to hear something about it, I will be glad to tell you. If you do not think it is pertinent, say so. This is the question from the audience, "Wouldn't the Public Health Service be doing a more efficient job if they disseminated information to the press regarding a weight reduction program for the obese rather than spending so much time on the Asian flu problem?" (Applause)

I take it for granted that you are clapping for the person who posed the question.

MODERATOR POLLACK: If there is no further discussion, we will terminate this part of the program.

Froment, R., Blanc, J., Gallavardin, L., and Perrin, A.: An Exact Sign of Massive Left Auricular Thrombosis: Permanent Disappearance of the Murmur and Thrill of Organic Mitral Insufficiency. Arch. mal coeur **50**: 289 (April), 1957.

A 30-year-old man with mitral stenosis showed a very loud systolic murmur and thrill near the heart apex. Between the ages of 36 and 40 there was progressive diminution of the intensity of the murmur, and between the age of 44 and death at the age of 48 no murmur could be heard. Signs of cerebral embolization appeared at the time the murmur began to disappear. Autopsy disclosed pure mitral insufficiency and thrombosis of the entire left atrium with the exception of a channel of about the same width as the mitral orifice. A second patient, who is still living, showed an almost identical clinical picture. The disappearance of the murmur is attributed to the disappearance of a major discontinuity of lumen in the path of the regurgitant blood stream.

LEPESCHKIN

CLINICAL PROGRESS

Theory and Practice in Acute Venous Thrombosis

A Reappraisal

By STANFORD WESSLER, M.D., AND DANIEL DEYKIN, M.D.

THE urgency of the physician's concern with acute peripheral venous thrombosis (phlebitis) clearly lies in the intimate but unpredictable association between clots in peripheral veins and death from embolization of these clots to pulmonary arteries. Although this relationship has been known for almost a century, past experience has failed to furnish any widely accepted or consistent approach to the management of phlebitis. Our purpose is to re-evaluate the problem of phlebitis on the basis of a critical review of published data and of our clinical, pathologic, and experimental observations. It is believed that a useful frame of reference can be derived from this presentation whereby a rational choice of therapy can be made in a large majority of clinical situations.

ETIOLOGY

After Harvey's experiments had dispelled the Galenian theory of the humours, Richard Wiseman was perhaps the first to apply the newly acquired knowledge of the circulation to the etiology of intravascular coagulation. In a passage remarkable for its prescience Wiseman in 1676 described the propagation of a thrombus and stated that intravascular coagulation was in part related to systemic alterations in the circulating blood.[1] This concept, however, was destined to dominate neither the investigations of Wiseman's day nor of subsequent generations.

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With the rise of Newtonian mechanics a new school of medical thinking developed. Disease was explained in terms of mechanical derangements in internal viscera. Thus, stagnation of the circulation during pregnancy was simply the result of uterine pressure on the iliac veins. John Hunter's description of phlebitis[2] in effect established local change, by which was meant septic inflammation, as the sine qua non in the etiology of venous thrombosis. This concept reached full flower in the writings of Cruveilhier,[3] who effectively opposed the idea that coagulation could represent anything but the effects of local change.

At a time when the theories of Hunter and Cruveilhier had attained universal acceptance, Rudolph Virchow[4] completed his monumental study of the pathology of the circulatory system. In language that is crisp, incisive, and exciting, Virchow crystallized the general principles of thrombosis, documented the concept of embolization, and enunciated the hypothesis that is still referred to as Virchow's triad: namely, that stasis, systemic alterations in coagulability, and local trauma and inflammation are causative factors of intravascular coagulation. Virchow's observations were extended by his associates and students[5–7] and were effectively summarized in a critical monograph by Welch[8] in 1899.

Although Virchow's triad has continued to be postulated as the principal mechanism of thrombus formation, the interdependence of these factors has never been adequately elucidated, and vascular injury has continued to be regarded as the principal cause of thrombosis. Since the studies of Bizzozero[9] numerous investigators have repeatedly observed that injury to a vein wall results in the adherence of platelets to the endothelium of the injured area, and that these platelets aggluti-

nate to form platelet thrombi. It has also been clearly shown that fibrin deposition follows the formation of platelet thrombi which can form even in incoagulable afibrinogenemic or heparinized blood.[10-12] Samuels and Webster,[13] using a modification of O'Neill's staining technics,[14] showed that the adherence of platelets to the vessel wall usually occurred at the intercellular cement line in the endothelium and that this reaction could be induced by degrees of trauma that by clinical standards might hardly be called injury. In fact, in some situations platelet deposition was seen to precede demonstrable anatomic change in the endothelial cell. Paterson and McLachlin[15] on the basis of postmortem examinations of incipient venous thrombi in serial sections concluded that obvious local injury or disease in the vein wall was not a factor in the precipitation of bland thrombi in the lower extremities. Sawyer and co-workers[16] have demonstrated that normal bioelectric potentials or injury currents across a vessel wall can induce local vascular thrombosis. They suggested that the recorded changes in electric potential are probably functions of metabolic alterations in injured cells and their damaged membranes.

On the other hand, other investigators,[17] have repeatedly emphasized the difficulty of routinely producing grossly visible thrombi in experimental animals despite severe local trauma. Moreover, when experimental clots do form, they tend to remain limited to the area of local injury, even though the endothelial damage is greater than that frequently found clinically. These observations suggest that thrombosis induced by purely local vascular injury can be easily contained by compensatory mechanisms; only when these mechanisms are overwhelmed or destroyed by some generalized disturbance can thrombosis proceed unchecked. In this regard the release of platelet thromboplastin by coagulation factors in plasma[18, 19] and alterations in microelectric phenomena may also bear some systemic as well as local causal relation to thrombosis. It is thus possible that the importance of local injury *alone* in the production of *clinical thrombosis* has been greatly overestimated.

The importance of vascular stasis in the etiology of clinical intravascular thrombosis is as well entrenched as that of intimal damage. Phlebitic episodes that complicate surgery, congestive heart failure, pregnancy, anoxia, polycythemia, and shock all share an element of vascular stasis. Prolonged and unusual degrees of immobilization induced by standing, sitting, or squatting frequently precede the onset of clinical phlebitis by 12 to 48 hours. This information can often be elicited only by careful, purposeful questioning. Numerous reports have implicated stasis in the precipitation of clinical phlebitis following prolonged sitting in air-raid shelters,[20] automobiles,[21] airplanes,[21] and during television programs.[22] These are, of course, uncontrolled observations and do not reflect any greater immobilization in patients developing phlebitis than occur in other individuals who do not demonstrate intravascular coagulation clinically. Nevertheless, that stasis is a factor in initiating phlebitis is difficult to deny. The questions that remain unanswered concern the nature of the changes induced by stasis and the reasons why only certain individuals develop phlebitic sequelae from relative immobilization. It is not known whether stasis acts by inducing local or generalized alterations at the endothelial cell membrane or through some change in the formed elements of the blood or components of circulating plasma. Furthermore, like local injury, stasis is so ubiquitous that it is difficult to believe that it alone can cause *extensive* thrombosis.

In the light of recent advances in our knowledge of the clotting mechanism, the significance of hypercoagulability in the initiation of intravascular coagulation has come under fresh scrutiny. The identification of each new clotting factor has raised the possibility that abnormalities in these factors might be found among patients with thromboembolism. It has been suggested, for example, that venous thrombosis in certain clinical states may result, among other abnormalities, from an increase in the proconvertin-convertin complex,[23-27] elevation of the prothrombin moiety,[27] or increased adhesiveness of the

platelets.[28] A causal relationship has not been demonstrated, however, between intravascular thrombosis and an alteration in any known clotting factor. As with stasis and local trauma, it is difficult to establish that hypercoagulability alone is adequate to produce extensive thrombosis. The concept that intravascular coagulation may, however, be induced by alterations in circulating blood *and* local stasis (with or without direct trauma of the vascular endothelium) is quite consistent with clinical experience. This concept would readily explain the development of leg vein thrombosis in association with trauma, infection, surgery, bed rest, delivery, acute myocardial infarction, congestive heart failure, blood dyscrasias, malignancy, metabolic disturbances, and the use of drugs as well as the occurrence of phlebitis in otherwise healthy individuals (primary thrombophlebitis). Such a viewpoint would allow the possibility that the hypercoagulable factor may differ in each of these conditions. This hypothesis, moreover, would emphasize that the site of the underlying disease responsible for the hypercoagulability may be at a distance from the site of clinical thrombosis where stasis exists and that local endothelial injury need not be a factor.

To approach this problem experimentally we chose to study intravascular coagulation within the isolated segments of the jugular veins of dogs. We had been impressed by the repeated statements that a stationary column of blood in a vein included between 2 carefully applied ligatures remains liquid for weeks.[9, 29] The experiments were carried out more than 80 years ago but review of the original reports did not indicate clearly whether or not clotting had occurred in these segments.[30, 31] It appeared to us that a study of what did happen in isolated endothelial-lined segments might provide a bridge between the growing knowledge of test tube coagulation and of the clotting process in a more physiologic environment. From our studies it was evident that although some clotting did develop within 20 to 90 minutes after a vein was isolated, it was incomplete after 8 hours and occurred more slowly than in blood in contact with the coated surfaces of tubes currently employed in various in vitro technics. Furthermore, a fibrin clot was deposited intravascularly prior to the demonstrable utilization of prothrombin, even though the blood was completely stagnant and the vascular segment cut off entirely from the circulation.[32]

These experiments emphasize the real but limited role played by endothelial injury and vascular stasis in the induction of massive intravascular thrombosis. To attack the problem of hypercoagulability, we attempted to accelerate coagulation within isolated canine vein segments by as physiologic an agent as we could discover. We selected serum for this purpose because it was a natural product of the coagulation process itself, had been successfully used as a blood substitute in man,[33] possessed clot-promoting activity in vitro,[34-36] and had induced thrombosis in animals.[37] It soon became evident that a large thrombus could be regularly produced in the following manner. A segment of a dog's jugular vein was freed from its surrounding structures and its tributaries were ligated. Heterologous canine serum was then infused into a distant antecubital vein. One minute later, when the infused serum had passed through the circulation, the previously freed jugular vein segment was gently isolated with small clamps. A large red clot forming a cast of the isolated segment routinely developed within 60 seconds. By this technic the systemic infusion of homologous canine serum induced a transient hypercoagulable state during which massive thrombosis rapidly developed in veins containing stagnant blood far removed from the site of injection. Stasis, endothelial injury, or hypercoagulability alone or in combinations other than stasis and hypercoagulability failed to induce massive clots. Further studies have shown that venous stasis need only be partial and that endothelial injury plays little if any part in the reaction.[38] This experimental study represents one of the few clearcut in vivo demonstrations that a transient state of hypercoagulability

can actually induce massive thrombosis. Much work will be required before this hypothesis can be fully validated. The experimental method, however, does provide a tool for studying, by bioassay and subsequently by chemical indentification, those factors responsible for a hypercoagulable state that can lead to intravascular thrombosis in man.

Diagnosis

When thrombosis of a peripheral vein is accompanied by local venous distention, tenderness, edema, discoloration, pain, and fever, the diagnosis is not difficult. Similarly, phlegmasia alba dolens presents little diagnostic challenge and phlegmasia cerulia dolens, a form of massive venous thrombosis that may occasionally be mistaken for acute arterial occlusion,[39] is usually easily recognized. However, less extensive venous thrombosis may present extraordinary diagnostic difficulties to even the most experienced clinician. Calf tenderness,[40] pain on dorsiflexion of the foot,[41] slight elevation of the postoperative pulse and temperature,[42] and minimal edema of the extremity are described by most authorities as the early evidences of deep venous thrombosis. Yet anyone who has seen patients with such symptoms knows how difficult they may be to evaluate. Dubious calf tenderness, which may be the only clinical expression of a potentially serious venous obstruction, is even less diagnostic and may be due to orthopedic defects, arthritis, myxedema, or myositis. Whether or not such minimal findings are labeled as venous thrombosis is often determined not so much by the facts as by the bias of the clinical observer.

Various physical signs or maneuvers have been recommended as an aid in the diagnosis of phlebitis.[43–45] None of these has as yet either stood the test of time or been widely accepted. Laboratory tests have been similarly unrewarding. Venography, which enjoyed a brief period of popularity,[46–48] has fallen from general use. The heparin tolerance test, although employed in some clinics,[49, 50] has not gained wide acceptance. Several investigators have described alterations in known clotting factors in disorders frequently associated with thromboembolic phenomena,[23–28] but correlations between biochemical abnormalities and clinical phlebitis have not been forthcoming. All these direct and indirect attempts at diagnosis have failed because there is still no reliable test for detecting the prethrombotic, incipiently thrombotic, or actively thrombotic state. Furthermore, the severity of the phlebitic symptoms cannot readily be correlated with the likelihood of symptomatic or lethal embolization.

Massive venous thrombosis is often not attended by recognizable pulmonary embolism, whereas minimal clinical evidence of a clot in a peripheral vein can be associated with a fatal obstruction in a pulmonary artery. This observation has led to a distinction between "phlebothrombosis" and "thrombophlebitis."[51] In the former the clot is believed to be the predominant aspect of the pathologic process and inflammation of the vein wall a secondary phenomenon; in the latter, the reverse is believed to obtain. It has been stated that the hazard of pulmonary embolism is greater in phlebothrombosis.[51] Actually the edema, cyanosis, pain, and fever that accompany some episodes of phlebitis may be related more to the extent of the venous obstruction than to actual inflammatory changes in the vein wall. In any event this classification appears to be of dubious prognostic value[52–55]; it may on occasion give rise to a false sense of security.

The physician's current position in relation to thromboembolic disease is analogous to the problem that would be posed by anemia without laboratory technics to measure the hemoglobin and hematocrit, and to count the red blood cells. Not only would the signs and symptoms of incipient or mild anemia escape detection, but it would be extremely difficult to differentiate the various anemias. For the present, the physician must regard thrombosis as an indivisible entity in which even the final outcome of the disease process can be observed in only an indeterminate proportion of cases. Finally, it is these problems in diagnosis that demonstrate how difficult it is to record the

true incidence of venous thrombosis—knowledge of which is so crucial for the evaluation of therapy.

Clinical Course

Few physicians would deny that venous thrombosis, difficult as it may be to diagnose on occasion, is also a common and usually benign disease. Such a clinical constellation obviously creates many obstacles to defining a practical and consistent therapeutic program. On the other hand, the unexpected fatality, occasionally in otherwise healthy individuals, strengthens the physician's desire to apply a therapeutic program to all patients suspected of having venous thrombosis.

There are 3 additional facets to the pathogenesis of venous thrombosis that have not received adequate recognition but that nevertheless influence the course of the disease to a profound degree. The first is that venous thrombosis has a definite if indeterminate incidence of recurrence. When a patient is first seen, it is not possible to predict in that individual whether a recrudescence may appear, where it may become clinically apparent, or how extensive and enduring it may prove to be.

Secondly, venous thrombosis is frequently a focal manifestation of a systemic disease. Evidence to support the systemic nature of venous thrombosis derives from patients who have multiple episodes or phlebitis in different areas of the body with or without underlying recognizable systemic disease. Recurrence of migratory superficial and deep phlebitis[56–61] in the extremities, venous thrombi in visceral and cerebral veins,[62–67] right atrial thrombi,[68, 69] and nonbacterial thrombotic endocarditis[70] are examples. In support of this concept we have released serum-induced thrombi from peripheral veins in normal dogs and have produced right-sided thrombotic endocardial lesions that resemble microscopically those found in human hearts.[71] It has been our experience, as well as that of others,[61] that primary, idiopathic, or spontaneous venous thrombosis is indistinguishable from the phlebitis occurring following injury, stasis, or during the course of a known disease.

Thirdly, the extent to which intravascular thrombi may dissolve spontaneously has not been adequately appreciated. Clinical observations of the natural history of venous thrombosis in superficial veins in man clearly indicate that obstructed vessels may in time become completely patent. Fibrinolytic activity in normal blood has been measured in vitro,[72, 73] and spontaneous increases in lytic activity have been observed in a variety of pathologic states.[74–77] It is also possible to augment the normal fibrinolytic activity of plasma by the introduction of specific activating compounds, and the dissolution of artificial clots in animals has been accelerated by these agents.[78, 79] Preliminary studies have suggested that the artificially induced activation of the normal lytic mechanism may dissolve clots in man.[79–81] Pari passu with the endothelialization of clot and the enlargement of preformed intervenous communications, clot lysis acts as an additional compensatory reaction to fibrin deposition. Spontaneous lytic activity, in this way, contributes to the generally benign course of venous thrombosis in man.

All these considerations relating to the diagnosis and clinical course of venous thrombosis indicate the extreme difficulty, in the present state of our knowledge, of a statistical approach to the clinical evaluation of therapy for phlebitis and may, in fact, account for the varying conclusions reached by different clinical investigators.

Pathologic Observations

It is perhaps not fully realized how meager has been the contribution of pathologic studies to the establishment of criteria for the incidence, etiology, and pathogenesis of venous thrombosis. The bulk of reported investigations has been based on cases of known pulmonary embolism and venous thrombosis.[82–85] They represent analyses of necropsy series in routine hospital populations and demonstrate a marked variation in the incidence of the 2 conditions. No pathologic criteria have been

provided by these studies for establishing the diagnosis clinically. This failure is related, in part, to the inaccuracy in the pathologic determination of the age of venous thrombi, which may vary greatly in actual or apparent age in different areas of the same thrombus, because of the rate of organization of the clot on the one hand and the deposition of new clot on the other. In addition, the varied prevalence of venous thrombi in the calf *and* of pulmonary emboli at autopsy makes even the establishment of death from embolization (in the absence of massive clot) an almost insoluble problem.

The pathologic difficulty is further complicated by the fact that clots initiated as platelet thrombi may originate or propagate by mechanisms quite distinct from those operative in the formation and evolution of thrombi initially rich in red blood cells. The possible contribution of the phenomenon of sludging of the blood[86] to the genesis of these latter clots remains unsettled. In our experimental studies the massive red clot that is formed by the infusion of serum and local venous stasis is of particular interest in that it consists, in essence, of a meshwork of fibrin in which cells are trapped; there is at the onset of formation no evidence of the lines of Zahn, and in its fresh state it cannot be distinguished either grossly or microscopically from a red postmortem clot.[87] After a number of days in situ, however, loss of red cell structure occurs, and the clot is gradually transformed into a hyaline mass showing varying degrees of organization. When small, single fresh clots, 4 to 6 cm. in length, are released from a peripheral vein into the pulmonary circulation, no hemodynamic alterations are produced and adherence to the pulmonary artery endothelium does not occur for days. These clots disappear from the pulmonary artery tree within 1 to 2 weeks of their formation.[88] Massive embolization of fresh clots, 100 to 200 cm. in length, has produced only transient hemodynamic alterations and only occasional small pulmonary infarcts. As in the case of the small clots, extensive reduction in the size of the massive emboli occurs within days after their release to the lung.[89] In contrast, when single clots, 4 to 6 cm. in length, are aged in a peripheral vein for 2 weeks prior to their release, relatively little reduction in clot volume is found upon examination of the pulmonary arteries examined 4 weeks after embolization.[89]

It is apparent that large amounts of fresh red thrombus can be rapidly removed from the circulation leaving only relatively small amounts of clot to became organized. Older clot is evidently handled with much less efficiency. It must be emphasized, however, that this type of clot induced by stasis is distinctly different, both in structure and genesis, from the platelet-rich clot resulting from endothelial injury, and it is possible that these 2 types of clots may also differ in their behavior subsequent to formation.

Although not always a safe procedure, nonetheless the temptation is strong to extrapolate experimental results to clinical experience. If clots of the stasis type are also produced in man, as seems probable from current postmortem studies in our laboratory, it might be very difficult, if not impossible, to distinguish some of them from postmortem clots at autopsy. Conversely, rapid lysis of such clots might conceivably account for some of the discrepancies between reported clinical findings and postmortem observations. Finally, the small organized residua found in the pulmonary arteries in some of the experimental animals resemble very closely, both grossly and microscopically, residua observed in man at the autopsy table, and could well originate in a similar fashion. It is believed that these experimental studies may offer a partial explanation for some of the false interpretations that result from attempts to correlate residual pathologic evidence of thrombosis at necropsy with clinical events.

Critiques of Therapy

In the practice of medicine acceptance of a new therapeutic technic is often determined by the accepted contemporary concepts of the disease. In such a situation the enthusiasm for therapy may inadvertently delay for dec-

ades a fresh look at the life history of the disease and a critical review of the therapeutic results. By 1934 the idea of phlebitis as a local disease and of pulmonary embolism as a tragic complication of surgery had become well established. Thus, when John Homans[90] focused attention on the occurrence of deep venous thrombosis in the surgically approachable veins of the calf and thigh and their role in the production of pulmonary emboli, his observations fell on fertile soil and a new era of interest in venous thrombosis was launched. A series of pathologic studies quickly confirmed the frequency of thrombi in the calf veins.[82–85] Following rapidly upon this increasing interest in venous thrombosis among surgeons, was a new awareness of the problem by internists, particularly concerning cardiac patients.[91, 92] An extensive surgical experience was rapidly accumulated by many clinics and indicated the efficacy of femoral vein ligation in the prophylaxis and treatment[42–52, 90, 93] of venous thrombosis of the lower extremity. Almost concurrently, other investigators suggested that heparin might be useful in treating phlebitis.[94–96] Shortly after the purification of Dicumarol by Link,[97] this anticoagulant, too, was used therapeutically.[98, 99] By 1945, proponents both of vein ligation and of anticoagulant therapy had accumulated favorable results in the treatment of venous thrombosis and pulmonary embolism and the battle was joined.

The recent amount of literature on the therapy of venous thrombosis has become enormous. Its most characteristic feature is a lack of agreement on the incidence and significance of the disease and on the response to therapy. Some of the reasons for these divergent opinions stem directly from what has already been said of the clinical behavior of venous thrombosis. It has been unfortunate that the new therapies for venous thrombosis had to be instituted when knowledge of both the pathogenesis of the disease and the sequential biochemistry of the coagulation mechanism was rudimentary. As a result, observations have been made largely by investigators partial to a particular mode of therapy. Many workers[100–103] were cognizant of the difficulties in diagnosing venous thrombosis and were aware of the pitfalls in accepting only recognized cases as representing the whole spectrum of the disease. The extraordinary care that the pathologist must take if he hopes to confirm diagnoses of pulmonary embolism has also been emphasized.[104]

Despite these admonitions, the literature has become increasingly full of poorly established claims and counterclaims. Early enthusiasms, by virtue of frequent repetition in many journals, have been accepted as facts. Statistics that have little validity go unchallenged and no clear picture of the disease process or its response to therapy has emerged. Amidst this confusion DeBakey's perceptive review[103] stands as a chastening influence on attempts to draw sweeping conclusions from limited clinical surveys of venous thrombosis, without precise statements concerning definitions and diagnostic criteria. DeBakey clearly pointed out the inordinate difficulties in assessing clinically the true incidence of phlebitis as well as the results of various treatments. His paper serves, in a sense, to summarize the 55-year period that followed Welch's earlier contribution on the same subject.

Vein Ligation

A clot in a peripheral vein represents a potential pulmonary embolus. Interruption of the venous channel proximal to the clot should remove this hazard. This premise has a compelling directness and simplicity: fortified by data on the frequency of lower-limb venous thrombosis, it has been a bulwark of the surgical approach to venous thrombosis. Although clearly of value in septic phlebitis, vein ligation fails to protect the patient in whom clots already exist proximal to the tie, or may subsequently form above the site of ligation.[105–110] It fails to obviate the fact that the ligation itself, by producing local intimal damage and vascular stasis, may predispose to clot formation distal as well as proximal to the tie.[38] It fails to prevent the possibility of the thrombotic process, moving through col-

lateral channels, by-passing the tie, and reaching the lung.[111] From unilateral superficial vein ligation to bilateral superficial vein ligation to common femoral and finally to inferior vena caval ligation cumulative surgical experience has indicated the limitations of the initial operative premise.[106, 108–114] Caval ligation, in one step, cuts off embolization from the lower extremity without much increasing the chance of thrombosis proximal to the tie. On the other hand, it does not answer the problem that one may be dealing with a generalized clotting tendency, and it represents a surgical procedure with slight but real mortality and disability.[115] To date, statistical studies have failed to show that bilateral, superficial, or common femoral vein ligation are of prophylactic or therapeutic value in diminishing the incidence of pulmonary embolism. Nevertheless, in individual instances, in which showers of pulmonary emboli have ceased following vein ligation, it is difficult to escape the impression that surgery has been helpful. For the present, however, it would appear best to think of vein ligation as a local adjunct in the treatment of a systemic disease.

Anticoagulant Drugs

Anticoagulants are currently believed by many to be the preferred alternative to vein ligation in the prophylaxis and treatment of venous thrombosis.[116–125] Although initially proposed for the treatment of a local process, these drugs have the theoretic advantage of blocking thrombus formation anywhere in the vascular tree. However, statistical clinical validation of the therapeutic efficacy of these drugs has not been established beyond question in the treatment of phlebitis itself. Just as the optimal site of vein ligation remains unsettled, so with anticoagulant treatment we find no agreement on the choice of drug, its effective dosage, its method of control, or its duration of administration. The search for new anticlotting compounds and new tests for their control are additional expressions of the lack of satisfaction with currently available agents and technics. Yet again, as with vein ligation, it is difficult to escape the evidence that in individual cases, anticoagulants have interrupted the process of recurrent pulmonary embolization.

One particular problem in thromboembolic disease that is not solved by anticoagulant therapy is the prevention of the breaking off of a thrombus from an organized aged clot formed prior to anticoagulant therapy. It is difficult to conceive how these agents can effectively prevent this phenomenon. It is believed that by the retardation of further clotting, the thrombus already present may be rapidly covered with endothelium and bound down to the underlying intima. The factors, however, that determine the cleavage of aged clots and the passage of embolic fragments to the lung are not clearly understood. Some failures of anticoagulant therapy may be anticipated until this process can be prevented.

Lytic Agents

Anticoagulant agents are effective by virtue of their inhibition of the further deposition of clot. It remains that when the anticoagulant is discontinued, thrombi formed prior to the institution of anticoagulant therapy will persist and that these may serve as a nidus for further clot formation. Thus, the availability of agents for dissolving clots suggests the early treatment of venous thrombosis with lytic agents alone or combined with anticoagulant therapy. Fibrinolytic compounds or substances that activate the normal fibrinolytic mechanism appear to offer a valid therapeutic tool, for these agents may induce clot dissolution in the pulmonary artery as well as in a systemic vein. In the past, compounds recommended for this purpose have had nonspecific proteolytic effects or have been toxic, so that they could be used neither effectively nor safely.[126, 127] With the advent of more highly purified compounds,[79–81] the development of lytic agents has reached the stage of practical clinical trial. However, the use of these drugs must also be viewed with caution until it has been demonstrated in man that fibrin can be dissolved without precipitating

hemorrhage from afibrinogenemia or significant alterations in other clotting components. Further caution is also warranted in that the dissolution of venous thrombi may itself promote pulmonary embolization. Even when these hurdles have been surmounted, the evaluation of lytic agents will have to overcome the same obstacle that has confronted vein ligation and anticoagulant therapy, namely, the difficulty of knowing whether thrombosis has occurred. Furthermore, it is already clear[89] that old organized thrombi have a greater resistance to dissolution by the normally acting lytic mechanism than do fresh clots. Evidence has also been obtained that induced fibrinolysis is more effective in fresh than aged thrombi.[79] Thus, one may anticipate that lytic agents will be most useful against the very clots that the body itself can handle most effectively.

Prevention of Stasis

Despite general agreement that stasis plays a significant role in the pathogenesis of venous thrombosis and despite increasing awareness of the hazards of bed rest[128] the evidence is conflicting that early ambulation has diminished the incidence of phlebitis.[108, 129–133] Elastic support can frequently alleviate some of the signs and symptoms of chronic venous insufficiency. This treatment has also been recommended for the prophylaxis of acute phlebitis.[134, 135] Although the theoretic advantage of increasing the rate of blood flow through decreasing the size of the peripheral venous pool is apparent, data are not available to indicate whether or not elastic support is of value in the treatment of acute phlebitis.

A Specific Program for the Practical Management of Acute Venous Thrombosis

Theory

As we have interpreted the entity of venous thrombosis, it represents a common, frequently systemic disease, manifest clinically by focal intravascular coagulation. The specific etiology is unknown, the diagnostic criteria are crude and unsatisfactory, and although the clinical course is usually benign and self-limited, it may be unpredictably recurrent and lethal. We have also implied that it is extremely difficult at present to validate statistically any specific therapeutic measure; this problem will not be significantly altered until an accurate test for thrombosis is devised.

An awareness of the state of current knowledge in itself provides little guidance to the physician called upon to treat the patient with phlebitis. He cannot await the ultimate delineation of the disease process; for, by withholding specific treatment, he makes a therapeutic decision as clearly as if he used a knife or a drug.

To construct a workable frame of reference for the clinical management of venous thrombosis within the limits of our present knowledge, we have formulated a general concept that has been helpful to us in the treatment of phlebitis. This concept is predicted on the *assumed* existence of a hypercoagulable state and hypothesizes that local vascular injury or stasis alone is inadequate to induce clinically significant venous thrombosis. The hypothesis states that individuals with clinically recognized intravascular clotting have a state of hypercoagulability, as yet not demonstrable, that predisposes them to thrombosis. Hypercoagulability may be due either to known or as yet unidentified alterations in one or more specific clotting constituents. These alterations may be induced by the liberation into the circulation of altered moieties from gravid uteri, traumatized tissues, necrotic foci, malignant neoplasms, or by systemic changes in plasma proteins. When the balance between clot formation and clot lysis is altered, a thrombus can be initiated and potentiated by a degree of stasis that would not *by itself* result in clot formation. Finally, hypercoagulability and vascular stasis may be systemic or local, transient, prolonged, or recurrent. With this formulation, which we have termed "the temporary thrombotic state,"[136] treatment becomes predicted upon neutralization of the hypercoagulability by retarding the deposition of further clot (anti-

coagulants); the dissolution of already formed fibrin (lytic agents); and upon the reduction of stasis through the cessation of procedures that favor immobilization and the correction of factors, such as shock, congestive failure, and a large peripheral venous pool, that favor retarded blood flow.

Since the status of lytic agents is still experimental and the correction of shock and congestive failure are well established on other grounds, the specific treatment of acute phlebitis is reduced at present to the neutralization of hypercoagulability by anticoagulant drugs and the decrease in vascular stasis by reduction of immobilization and the use of elastic supports. Within this formulation vein ligation and other measures proposed for the relief and control of venous thrombosis become ancillary therapeutic tools.

Thus, the major questions posed by phlebitis are: In whom should anticoagulant therapy or elastic support be used, in what form, and for how long; and under what circumstances is vein ligation indicated?

Practice

Based on the concept of the temporary thrombotic state and on observations of the clinical course of a large number of patients with phlebitis, the following details of management have been evolved by us during the past 5 years. This program represents current therapeutic practice on the medical ward service at the Beth Israel Hospital. The reader is reminded that the validity of this regime cannot yet be supported solely by statistical data and that no convincing evidence is available to demonstrate the superiority of this program over alternative plans currently employed by other clinics. It meets the problem of venous thrombosis by providing a simple positive therapeutic regime consistent with the known experimental, pathologic, and clinical data.

For initial episodes of acute superficial or deep phlebitis, watchful waiting for 12 to 24 hours is usually justified. Paradoxical as it may appear, bed rest is employed without immobilization and with elevation of the involved extremities if edema is present. If the phlebitis appears to progress within this interval, anticoagulant therapy is instituted, if no hemorrhagic tendency exists. If, on the other hand, no progression or regression of the lesion is noted, a gradual increase in activity is immediately begun and is continued, if symptoms do not recur. With ambulation a properly fitted cotton or nylon elastic lower-leg stocking is prescribed, even if the phlebitis originally occurred in the thigh, provided that co-existent severe peripheral arterial insufficiency is not also present. The majority of patients will respond to this simple regime in which the use of the elastic support is continued for a 4-week period during those hours in which the patient is ambulatory. Although such a policy invites the risk of an occasional pulmonary embolus, our experience appears to justify such a program, *provided* the patient is carefully observed during the initial few days for symptoms or signs of progression or spread of the disease. There are, of course, instances of spontaneous massive iliofemoral phlebitis, or less extensive phlebitis, in patients with acute myocardial infarction or congestive heart failure, or in individuals in postoperative or post-traumatic situations requiring immobilization, whom the physician might reasonably elect to treat immediately with anticoagulant drugs because of the presumed serious danger of embolization.

On the basis of our own investigations[137, 138] and the experience of others,[139–142] it would appear that heparin is a broader and more effective anticoagulant than Dicumarol and its related compounds at least for the first few days of treatment. Thus, once anticoagulant therapy is decided upon, treatment with heparin is started. If only the acute episode of phlebitis is to be treated with anticoagulant drugs, this is accomplished with heparin alone. Heparin at present is administered intravenously every 4 hours by means of an indwelling plastic catheter inserted into a superficial forearm vein.[143] The dose of heparin, which may range from 25 to 100 mg. at each injection, is adjusted with the aid of clotting times,[144] so that a given amount of

drug will approximately double the initial clotting time at the end of 4 hours.[138] After this dose is established, clotting times are determined once daily to avoid a significant build-up of the anticoagulant effect and to allow for variations in heparin requirements during the course of treatment. In the immediate postoperative period, when anticoagulant therapy may be especially hazardous, heparin has been administered on a 2 hour schedule to avoid peaks of hypocoagulability for the first 3 to 5 days and thereby presumably to diminish the risk of hemorrhage. For those initial episodes of phlebitis in which an anticoagulant is administered, heparin is continued for 8 to 10 days. This interval was determined in part by the time required for complete subsidence of the signs and symptoms of active phlebitis and also by the time required for firm adherence to the vein wall of experimentally produced bland thrombi.[145] Ideally, the patient is then observed for 48 hours without heparin before discharge from the hospital.

We are aware of the recommendations of others for constant intravenous infusions of heparin, intravenous injections of heparin every 8 hours without control of the clotting times and the intramuscular, subcutaneous, and sublingual use of heparin in various menstrua.[146–162] We are also appreciative of the nonhemorrhagic hazards of heparin therapy.[163–165] Based on considerations of maximal antithrombotic effect, reliability, safety, and unpleasant side reactions as well as an analysis of our own clinical experience in which thrombotic breakthroughs on heparin have occurred, we believe the intravenous use of heparin on a 2 or 4 hour schedule to be at least as satisfactory as any technic of heparin administration currently available for the short-term treatment of phlebitis.

After discharge the patient is advised to wear a properly fitted elastic support for 1 or 2 months. All patients with initial episodes of phlebitis, whether treated with heparin or not, are given detailed instructions about the avoidance of immobilization in their daily activities as a prophylaxis against recurrence. Specifically, patients are cautioned against prolonged sitting in an easy chair, at a desk, in a theater, airplane, train, or automobile, against prolonged immobilized standing behind a sales counter or a factory machine, and against sitting cross legged while doing household or gardening chores.

In patients with *recurrent* superficial or deep venous thrombosis or migratory phlebitis, the wisest course, in general, is anticoagulant therapy; for these individuals have now presented evidence of the need for more sustained and prolonged therapy in conformity with the concept of the hypercoagulable state, particularly if the recurrence is within days to weeks after the initial episode. In patients with recurrent phlebitis, heparin therapy is instituted initially and continued until symptoms of discomfort disappear. At this time Dicumarol is added and the 2 drugs are administered concurrently for 1 week.[166, 167] Heparin is then stopped and the patient is discharged with Dicumarol, controlled eventually by weekly prothrombin determinations. The patient is also given a card stating that he is on anticoagulant therapy. Dicumarol dosage is currently regulated by the Rosenfield and Tuft[168] modification of the Quick prothrombin time. The prothrombic activity is kept between 10 and 20 per cent of normal. The basis for choosing these levels of activity, as well as other details pertaining to the measurement of prothrombic activity, has been well described by Alexander and coworkers.[169, 170]

We limit the prolonged use of Dicumarol to a period of 4 to 6 months unless acute phlebitis recurs at that time. If after discontinuance of the drug phlebitis recurs, anticoagulant therapy is resumed, this time for a period of approximately 12 months. After the drug is stopped, elastic support is continued for several more months and the avoidance of prolonged stasis is again stressed. We have no evidence that Dicumarol is superior to other comparable drugs; we have continued to use it because of our familiarity with its action and our ability to control its activity.

Of course one of the unresolved problems

in Dicumarol therapy is the inability to equate the anticoagulant defects induced by the drug with its antithrombotic effects. The dissociation between the coagulation defect and the antithrombotic effect of Dicumarol has been demonstrated experimentally,[171] and clinical experience has repeatedly shown that thrombosis may occur even when the 1-stage over-all prothrombic activity is below 15 per cent of the control value. Several investigators have emphasized the limitations of this test in regulating the dose of Dicumarol and some have suggested alternative guides to therapy.[50, 166, 172–175] Until acceptance of one or more of these alternative technics becomes established, we think that control of limited, long-term Dicumarol therapy for patients with recurrent phlebitis can be accomplished with the 1-stage method.

Although venous thrombosis may recur anytime after the cessation of anticoagulant therapy, it is not uncommon for phlebitis to be recognized clinically within 24 to 48 hours after heparin administration is stopped or 5 to 15 days after Dicumarol therapy is discontinued. This phenomenon has been attributed by some to a compensatory "rebound" phenomenon or hypercoagulability induced by the sudden withdrawal of the anticoagulant drug.[176] Although this concept is not supported by adequate data, it is certainly a tenable viewpoint, though no more so than the alternative hypothesis that the patient with recurrence after cessation of anticoagulant therapy has merely returned to the state of hypercoagulability existing prior to treatment. Since one cannot with any assurance choose between these two alternatives, it is, in our opinion, best to discontinue each drug gradually with the goal of decreasing the likelihood of a rebound phenomenon, should such an entity exist. Accordingly, heparin dosage is decreased stepwise by 5 mg. every 4 hours and Dicumarol (in patients who have received the drug for several months) is decreased in such a manner that prothrombic activity does not return to normal for 2 to 3 weeks.

If a patient is believed to have sustained a pulmonary embolus, with or without peripheral phlebitis, he is treated in a manner comparable to the treatment of a patient with recurrent venous thrombosis.

On rare occasions the problem is posed of using anticoagulants for the treatment of phlebitis during pregnancy or at a time when major surgery is necessary. The literature on this subject is limited. Occasional reports of hemorrhagic manifestations in the fetus have been published.[177] On the other hand, data from several clinics indicate that anticoagulants may be safely employed during major surgery.[178–180] There are also data indicating the feasibility of regional heparinization.[181–184] Nevertheless, we have, to the present time, avoided using anticoagulant drugs during pregnancy or surgery. With regard to surgery, we have attempted to defer operation or, if this was not justified, to stop drug treatment and to ligate both common femoral veins or the inferior vena cava prior to or concomitant with the surgical procedure. If pulmonary embolism occurs following surgery, we use heparin on a 2 hour schedule intravenously for the first 3 to 5 postoperative days and thereafter on a 4 hour schedule.

Vein ligation is ordinarily not used prophylactically but is invoked only after venous thrombosis has occurred. Currently its use is restricted to patients in whom the potential vein source may be septic, in whom anticoagulants cannot be administered with safety and in whom the drugs have been shown to be ineffective in preventing clots. Our choice of a site for ligation is either bilateral common femoral vein interruption or inferior vena caval ligation below the renal veins. Although we believe that caval ligation is the more effective procedure,[185] need not produce permanent detrimental effects,[186] and can be successfully carried out despite congestive heart failure,[187, 188] selection of the appropriate site in an individual patient must be made on the basis of the specific findings and the relative hazards of the disease and its treatment.

The vast majority of patients, as indicated above, obtains symptomatic relief and clinical subsidence of their phlebitis with bed rest.

When persistent pain or edema is present, elevation of the extremity is frequently helpful. The application of heat, or occasionally cold, to the phlebitic extremity may also ease pain and discomfort. Occasionally it is necessary to give mild analgesics such as aspirin or, rarely, codeine or meperidine (Demerol) during the first few days of the illness. These agents are used only for symptomatic relief.

Embolectomy and autonomic blockade for acute venous thrombosis or pulmonary artery obstruction[102, 189–198] have not yielded convincing results and do not merit further consideration at this time.

There has been a recent vogue for the use of nonspecific anti-inflammatory agents such as trypsin and phenylbutazone in the treatment of the thrombus or the pain and edema produced by phlebitis in some patients.[199–204] Usually these symptoms are not severe and subside spontaneously following a few days of bed rest and leg elevation. Furthermore, these drugs are not without hazard.[127, 205–207] We have therefore avoided them, despite the currently favorable claims in the literature. Their value will be established only by further clinical trial.

Antibiotics have no place in the routine treatment of venous thrombosis. They should be restricted to the management of phlebitis complicated by infection, and the choice of antibiotics should then be determined by the drug sensitivity of the invading organism.

One additional problem that each physician must resolve when he sees, for the first time, a patient with idiopathic phlebitis, is whether he should undertake extensive investigations to uncover malignant disease. Since the original observation of Trousseau,[208] convincing evidence has been marshalled by many investigators[209–212] that a relationship exists between cancer and phlebitis. Idiopathic venous thrombosis may be the first clinical manifestation of an occult neoplasm,[213–215] and carcinoma of the pancreas, lung, and stomach are among the most frequent offenders.[216] Isolated "cures" of a carcinoma have been suggested in individual instances in which the phlebitis led to the finding of an operable malignant lesion.[215]

On the other hand, in our experience, most patients with idiopathic phlebitis do not have cancer; among those who do have both diseases some evidence of malignant disease is common by the time phlebitis appears; and finally, no "cures" of carcinoma detected after the onset of phlebitis have been observed. During the past 5 years at the Beth Israel Hospital, where alertness to the diagnosis of phlebitis is widespread among both house staff and visiting physicians, we are not cognizant of a single patient with carcinoma, in whom this diagnosis was discovered after the development of clinical phlebitis and in whom the surgeon found an operable, much less a "curable," lesion. Finally, since both phlebitis and carcinoma are common diseases, the occasional report of the onset of phlebitis providing the clue to a "curable" malignant lesion, may be fortuitous. Phlebitis may certainly herald a malignant process, but the announcement is almost invariably late.

On the basis of this type of recapitulation of the available data, our current policy is to subject patients with idiopathic phlebitis to a detailed history and a complete physical examination including careful palpation of the thyroid, breast, abdomen, pelvic organs, prostate, and lymph nodes. Laboratory work is limited to a urinalysis, hemoglobin, white blood count, differential count, stool examination for occult blood, and posteroanterior and lateral chest roentgenograms. These procedures may alert the physician to possible bleeding tendencies that might influence his choice of anticoagulant therapy. The chest roentgenogram, aside from offering evidence for a primary or metastatic carcinoma, does provide baseline information for evaluating present or future episodes of possible pulmonary emboli. The only additional procedure that may be included is a roentgenographic examination of the upper gastrointestinal tract which, beyond offering suggestive evidence for pancreatic or gastric malignancy, may provide useful information concerning esophageal varices or an old duodenal ulcer that might again influence the use of anticoagulant drugs. The plan outlined above may be justified as part of the proper study of the

majority of patients with idiopathic venous thrombosis, quite apart from any light that might also be shed on an underlying cancer. If it is negative, further studies designed to detect an operable cancer are no more justified in these patients with phlebitis than in the population at large.

Case Reports

Case 1. Recurrent Peripheral Superficial and Deep Phlebitis Precipitated by Stasis or Mild Trauma. Treated with Heparin, Dicumarol, and Elastic Support. No Chronic Venous Insufficiency, No Pulmonary Emboli, No Underlying Heart Disease or Malignancy

A 56 year old man noted the onset of pain in the left instep 24 hours after a prolonged period of sitting. Despite bed rest, pain persisted and was followed in the subsequent 48 hours by left-calf tenderness and ankle edema. Because of these symptoms the patient was hospitalized for anticoagulant therapy.

During a 2 year interval, from 5 to 3 years prior to hospitalization, this patient had experienced 2 episodes of deep and 1 episode of superficial lower leg phlebitis, each precipitated by acute "ankle sprains." These were treated with anticoagulants and the patient never developed evidence of pulmonary embolism, heart disease, peripheral arterial insufficiency, or residual peripheral venous insufficiency. He had been wearing elastic stockings prophylactically for the past 3 years. During the past year the patient had noted "heart burn" and slight dysphagia in relation to meals.

Examination on entry was within normal limits except for point tenderness over the left instep, minimal left ankle edema, and a tender palpable left saphenous vein.

The following studies were normal: urinalysis, blood count, sedimentation rate, stool guaiac, glucose tolerance test, nonprotein nitrogen, calcium, phosphorus, acid and alkaline phosphatase, uric acid, electrocardiogram, chest roentgenogram, barium enema, and intravenous pyelogram. Roentgen examination of the upper gastrointestinal tract showed a medium-sized hiatus hernia without reflux, and a cholecystogram revealed cholelithiasis without gross disturbance of the concentrating capacity of the gallbladder.

Immediately after admission the patient was started on intravenous heparin therapy. Forty-five milligrams of heparin every 4 hours were required to double the control clotting time immediately prior to the next dose of anticoagulant. The signs and symptoms of phlebitis subsided in 3 days at which time the patient was given elastic stockings and was permitted to walk. Dicumarol therapy was then started and after the prothrombic activity was in the therapeutic range for several days, heparin was discontinued and the patient was discharged on maintenance Dicumarol therapy 12 days after entry.

Prothrombic activity was maintained between 6 and 15 per cent of the control value for the first month and between 15 and 30 per cent for the ensuing 3 months without a recurrence of phlebitis.

Two months after the Dicumarol was discontinued the patient noticed the onset of left-calf tenderness 24 hours following a day of prolonged sitting, despite the use of elastic stockings. This fifth episode of phlebitis subsided spontaneously after bed rest for 48 hours without anticoagulants, and the patient has remained free of a recurrence of phlebitis for the ensuing 2 years.

Comment. This patient represents a common example of recurrent migratory phlebitis without recognized underlying disease. Venous thrombosis was invariably precipitated by prolonged stasis or mild injury in the ankle area. Heparin therapy was given because the phlebitis did not respond to bed rest and long-term Dicumarol therapy because of the past history of recurrent phlebitis. The investigation for malignant disease was undertaken because of the gastrointestinal symptomatology.

Case 2. Unilateral Idiopathic Iliofemoral Phlebitis with Probable Recurrent Pulmonary Emboli. Controlled at First Only with Large Doses of Heparin. Subsequently Treated Successfully by Inferior Vena Caval Ligation

This 62 year old man was hospitalized because of severe stabbing pain in the left leg of 1 week's duration. The pain was aggravated by standing or walking and relieved by rest in the supine position. The past history included renal lithiasis 27 years ago, angina pectoris 5 years ago, and symptoms of prostatic obstruction and low back pain for several months before entry. There was no history of congestive heart failure, arrhythmia, or acute myocardial infarction.

Examination on entry revealed an emphysematous chest with clear lung fields and normal cardiac findings. There was a right inguinal hernia. The findings in the right leg were entirely negative. In the left leg the pedal pulsations were normal but there was definite posteroanterior calf tenderness with a positive Homans' sign and ankle edema.

Urinalysis was negative except for a trace of albumin. The hemoglobin was 10 Gm. with a hematocrit level of 35; the white count was 14,000

with a normal differential. Stools were repeatedly negative for occult blood. Fasting blood sugar, nonprotein nitrogen, total protein, albumin-globulin ratio, alkaline and acid phosphatase, bilirubin, amylase, cholesterol, thymol turbidity, and bromsulfalein retention were normal.

The patient was started on 75 mg. of heparin every 6 hours. The phlebitis became more extensive with massive edema, cyanosis, and pain in the leg and thigh. On the sixth hospital day, an episode of pulmonary edema occurred. The heart at this time was dilated when compared with a previous roentgenogram. The electrocardiogram was normal. The heparin schedule was changed to 50 mg. every fourth hour without doubling the clotting time, and on the eighth hospital day pulmonary edema occurred again. At this time there were electrocardiographic changes suggestive of acute myocardial ischemia although there was no chest pain. The heparin dosage was increased to 70 mg. every 4 hours at which level the clotting time was twice the control value 4 hours after the administration of heparin. Pulmonary edema did not recur and the phlebitis subsided. The heart size returned to normal. At no time were pulmonary emboli or pulmonary infarcts visualized by roentgenogram. Because of the questionable electrocardiographic findings and the episodes of pulmonary edema, the patient was treated as if he might have had an acute myocardial infarction and congestive heart failure. Because of the possibility of an underlying malignant lesion suggested by the persistent phlebitis, anemia, and back pain, additional studies were begun 26 days after entry. Roentgenograms of the entire gastrointestinal tract, cholecystogram, intravenous pyelogram, and bone marrow examination were all within normal limits. Since the patient was doing well, an attempt was made to reduce the heparin dosage preparatory to the institution of Dicumarol therapy. When the heparin dosage was decreased to 50 mg. every 4 hours, there was a definite flare-up of the phlebitis, which cleared when the dosage was raised again to 60 mg.

Thirty-seven days after entry, a transperitoneal ligation of the inferior vena cava was performed. The vena cava was free of clots but there was some thrombosis of the left iliac vein. Careful exploration of the abdominal viscera including the pancreas, spleen, and liver was negative. The right indirect inguinal hernia was reduced and the right internal abdominal ring closed.

Postoperative edema was successfully controlled by wrapping both legs with ace bandages up to the groin. There was no recurrence of acute phlebitis. After the abdominal surgery the patient was discharged with an indwelling urinary bladder catheter. Six weeks later the patient was rehospitalized for an uneventful prostatectomy without recurrence of the phlebitis. He has remained active and well during the subsequent 3 years and has not developed congestive heart failure.

Comment. This patient clearly had a more fulminating phlebitis than was present in case 1. It is probable that the episodes of pulmonary edema represented showers of pulmonary emboli that subsequently disappeared from the pulmonary artery tree. The need for an *adequate* amount of heparin is well exemplified. Caval ligation was chosen because it appeared that the thromboembolic disease would probably not be contained by Dicumarol alone and that the omission of even one dose of heparin, necessary for determination of the prothrombin time, might precipitate pulmonary edema. Because of the extent of the phlebitis, femoral vein ligation was considered inadequate. The transabdominal approach to the vena cava was selected because of the strong belief that a malignant process was present and because of the need to repair the inguinal hernia before the edema induced by the caval ligation became significant. It appears likely that therapeutic improvement was derived from vein ligation in this patient.

Case 3. Recurrent Superficial and Deep Phlebitis without Pulmonary Emboli in Patient with Metastatic Pancreatic Carcinoma. Phlebitis More Easily Controlled with Heparin than Dicumarol

A 52 year old man with intermittent claudication for 8 years was hospitalized because of right-calf pain. Six days prior to entry and 3 days after shoveling snow he developed a "charley horse" of the right leg. This leg pain persisted until entry without swelling. There was a brief episode of sharp left chest pain 24 hours before admission.

Eight months prior to entry the patient had a roentgenogram of the upper gastrointestinal tract at another hospital because of "heart burn." The findings were negative. During the 6 months prior to entry there had been a 10-pound weight loss without impairment of appetite.

Examination on entry was essentially within normal limits except that no pulses were palpable below the femoral arteries. There were marked pallor on elevation and delayed rubor on dependency of the left leg. There was definite posteroanterior tenderness in the right calf and in the medial aspect of the right thigh. There was no edema and no tenderness over the left lower ex-

tremity. The skin nutrition of both feet was good.

A urinalysis, complete blood count, and sedimentation rate were normal. The stools were negative on several occasions for occult blood. The nonprotein nitrogen, uric acid, phosphorus, calcium, alkaline phosphatase, total protein, albumin-globulin ratio, electrocardiogram, chest roentgenogram, plain film of the abdomen, and glucose tolerance test were all within normal limits.

The patient's course was essentially benign and afebrile. Intravenous heparin by catheter was started; 55 mg. every 4 hours was required to double the control clotting time. The right leg pain subsided in 3 days, the patient was allowed to ambulate, and he was given elastic stockings and maintained on heparin for 10 days, when Dicumarol was substituted without incident. It was planned to continue the Dicumarol for 4 months, not merely because of the phlebitis, but because he had arterial disease in the extremities and had had a possible, although unproved pulmonary embolus. At the time of discharge the prothrombic activity was 9 per cent of normal.

For 2 weeks the patient's prothrombic activity was maintained at 10 per cent of normal. Four days after discharge, however, the patient noted for the first time the onset of crampy lower abdominal pain, aggravated by walking and relieved by sitting or lying. Nine days after discharge a roentgenogram of the upper gastrointestinal tract revealed a filling defect suggestive of carcinoma of the stomach.

On reentry a single hard 1 cm. node was felt in the left supraclavicular area. Following intravenous vitamin K_1 to neutralize partially the coagulation defect induced by Dicumarol, the node was excised and found to contain adenocarcinoma. Twenty-four hours later, phlebitis recurred in the left calf and both heparin and Dicumarol were resumed. After 6 days, with a prothrombic activity at 10 per cent of normal, the former drug was discontinued. Within several hours after cessation of heparin therapy the right calf phlebitis recurred; and the patient again received heparin for 2 weeks with subsidence of the thrombosis. A second attempt to change from heparin to Dicumarol was followed by a recurrence of right calf phlebitis and heparin therapy had to be reinstituted. While on heparin therapy the patient had another recurrence of phlebitis in the right leg, this time associated with massive edema, redness, and pain of the entire extremity. It was realized at this time that there had been a sharp increase from 65 to 85 mg. every 4 hours in the amount of heparin required to double the patient's clotting time. With this higher dosage the phlebitis subsided although the patient continued to have crampy abdominal pain and developed anemia severe enough to require transfusions. Two months after this second admission the patient was for the first time successfully changed from heparin to Dicumarol without recurrent phlebitis and discharged from the hospital.

The patient remained at home for 2 weeks at a prothrombic activity of 10 to 15 per cent without recurrence of a phlebitic episode. Readmission was necessary, however, because of severe abdominal pain and anemia not controlled by narcotics and transfusions. Following reentry the patient failed rapidly and died, despite supportive measures.

The necropsy findings included (1) carcinoma of the pancreas with abdominal metastases, (2) acute pulmonary edema and bronchopneumonia, right lower lobe, (3) atherosclerosis of the coronary arteries, thoracic and abdominal aorta, and (4) bilateral thrombophlebitis of the femoral veins.

Comment. This case is an example of phlebitis complicating widespread metastatic pancreatic carcinoma. It is unlikely that recognition of the carcinoma at the initial hospitalization would have resulted in finding an operable lesion. The difference between heparin and Dicumarol in controlling this patient's phlebitis is interesting. This experience has not been uncommon for us. This case also emphasizes that there is no such thing as a "standard" dose of heparin for a patient. Not only will the dose vary from patient to patient, but in any particular patient the required dose of heparin may vary daily. Failure to recognize this phenomenon accounts for many instances in which anticoagulant therapy is erroneously stated to have been inadequate to control thromboembolic episodes. Elastic stockings were used despite the arterial disease, because the ischemia was not severe and skin nutrition was good.

Case 4. Recurrent Pulmonary Emboli in Patient with Phlebitis and Right Heart Mural Thrombi

A 70 year old woman was hospitalized because of a 3 day episode of fever, tachycardia, cough, dyspnea, hemoptysis, and left calf pain. For several months preceding the present illness the patient had been hospitalized at a mental institution and had received electric-shock therapy because of psychotic behavior.

Examination on entry revealed a temperature of 102 F., signs of consolidation in the right lower

lobe, and basal rales on the left. The heart was enlarged and fibrillating but there were no murmurs. All peripheral pulses were palpable in the left leg; no pulses were palpable in the right leg below the femoral, and this extremity was markedly cooler than the left. A warm, tender, distended varix was found on the right lower leg and on the right medial thigh. There was no edema.

Laboratory findings included a negative urinalysis, normal hemoglobin and white count, negative stool guaiac, and a normal glucose tolerance curve. Culture of the sputum was negative for respiratory pathogens. Chest roentgenograms showed cardiac enlargement and a pulmonary infarct at the right base. Electrocardiographic tracings showed atrial fibrillation and abnormalities suggestive but not diagnostic of acute myocardial infarction.

The patient responded well to heparin intravenously. Because of her marked emotional instability it was decided not to treat her on an ambulatory basis with Dicumarol. Vein ligation was not performed because of the arterial insufficiency in the right leg.

The patient did well for 2½ weeks after discharge until she suddenly became dyspneic with a productive cough, fever to 101 F., and anorexia.

Upon re-admission the patient was dyspneic, cyanotic, and dehydrated. There were dulness and diminished fremitus at the right base posteriorly, but no rales. There were inspiratory rales at the left base. The heart was enlarged; there were no murmurs. There was no edema or calf tenderness and again no pulses were palpable in the right leg below the femoral. The right lower extremity was cooler than the left.

The white count, which was 27,700 on entry, dropped to a normal range with a normal differential. Cultures were negative for respiratory pathogens and tubercle bacilli. Repeated electrocardiograms showed atrial fibrillation, but no evidence of acute myocardial infarction. The chest roentgenogram showed an extensive scar of the old infarct at the right base. The interlobar pleura on the right was thickened; the heart was dilated, especially the right ventricle. The hilar shadows were large with relative peripheral pulmonary oligemia suggesting marked elevation of the pulmonary arterial pressure. Subsequent roentgenograms showed consolidations in the right and left midlung fields suggestive of pulmonary infarcts.

On entry the patient was given intravenous fluids, additional digitalis, and mercurial diuretics as well as oxygen. The diagnosis of pulmonary infarction was subsequently supported by the development of a pleural friction rub in the right posterior lung field and right calf tenderness. Intravenous heparin was started every 4 hours but, despite doubling of the clotting time, the patient continued to have recurrent fever spikes with chest pain, friction rubs, pleural fluid, and hemoptysis. Heparin was nevertheless continued and the signs and symptoms of pulmonary embolism gradually subsided although dyspnea and orthopnea persisted. Two unsuccessful attempts were made to convert the atrial fibrillation to a regular sinus rhythm with quinidine. Dicumarol was added and after several days heparin therapy was stopped. While on Dicumarol, however, the patient had recurrent pleuritic chest pain and a friction rub in the left axilla. Heparin was therefore resumed and the Dicumarol discontinued. However, despite doubling of the clotting time at the 4 hour interval, the patient suddenly died on the fiftieth hospital day.

At necropsy the findings included (1) multiple pulmonary infarcts in 3 lobes, (2) multiple pulmonary emboli, organizing, all 5 lobes, (3) mural thrombi in right atrial appendage and right ventricle, organizing, (4) marked localized myocardial fibrosis, posterior apex of the left ventricle, (5) bronchopenumonia, and (6) healed gastric ulcer. The lower aorta and iliac arteries and veins were normal and there was no obstruction in the upper portion of the femoral artery or femoral veins.

Comment. During the first hospitalization it appeared that this patient had a myocardial infarct, a superficial phlebitis, a pulmonary infarct, and an embolus to the right popliteal artery. Because of the arterial insufficiency in the right leg the right femoral vein was not ligated; because the emotional instability would make ambulatory anticoagulant therapy hazardous, treatment with Dicumarol was not instituted. On the second admission multiple pulmonary infarcts preceded the phlebitis. It was believed that heparin was preferable to vein ligation because of the likelihood (reinforced by the probable myocardial infarct and the peripheral arterial embolus) that the pulmonary emboli were coming from the right heart. Necropsy confirmed this assumption. No explanation is available for the left ventricular fibrosis unless this patient's blood were indeed hypercoagulable and a thrombus formed on an atheroma in a coronary artery and was subsequently dissolved. Review of this case sug-

gests that no currently available therapy would have prevented the fatal outcome.

Summary

The purpose of this review has been to outline the basis for proposing, and the details for implementing, a rational and consistent plan of therapy for the management of acute venous thrombosis. We have interpreted the entity of venous thrombosis as representing a common, frequently systemic disease, clinically manifest by focal intravascular coagulation. Concerning this disease, the specific etiology is unknown, the diagnostic criteria are crude and unsatisfactory, and although the clinical course is usually benign and self limited it may be unpredictably recurrent and fatal. We have also inferred that the difficulties in statistically validating any specific therapeutic measure are, for the present, extremely great, and that this problem will not be significantly lessened until an accurate test for thrombosis is devised.

To construct a workable frame of reference for the clinical management of venous thrombosis within the limits of our present knowledge, we have formulated the concept of the temporary thrombotic state. Treatment is based upon the neutralization of hypercoagulability by anticoagulant drugs and upon a reduction of venous stasis by the removal of immobilization and a decrease in the size of the peripheral venous pool by elastic support. Various aspects of this therapeutic approach are described in detail and illustrated by selected case studies.

Summario in Interlingua

Le objectivo del presente revista es delinear le bases del proponimento e le detalios del execution de un programma systematic e rational in le regime therapeutic in casos de acute thrombosis venose. In isto, le entitate thrombosis venose es prendite como un commun e frequentemente systemic morbo que se manifesta clinicamente per focal coagulation intravascular. Pro iste morbo le etiologia specific non es cognoscite, le criterios diagnostic es crude e pauco satisfactori, e ben que le curso clinic es usualmente benigne e auto-limitatori, le morbo es a vices recurrente sin prediction possibile e pote devenir mortal. Il etiam pare esser evidente que al tempore presente omne essayo de establir, per medio del statistica, le valor therapeutic de un mesura specific es ancora extrememente difficile e que iste problema non pote resolver se usque un precise test pro thromboses ha essite disveloppate.

Pro construer, intra le limites del presente cognoscentias, un practic schema de standards pro le maneamento clinic de thrombosis venose, nos ha presentate le concepto del "stato thrombotic temporari." Le tractamento es basate super le neutralisation del hypercoagulabilitate per medio de drogas anticoagulante e super le reduction del stasis venose per le elimination del tendentia immobilisatori e le reduction del peripheric accumulation venose per medio de supporto elastic. Varie aspectos de iste methodologia therapeutic es describite in detalio e illustrate per studios de casos seligite.

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ABSTRACTS

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ATHEROSCLEROSIS

Selye, H.: Prophylactic Treatment of an Experimental Arteriosclerosis with Magnesium and Potassium Salts. Am. Heart J. **55**: 805 (June), 1958.

Studies in rats are presented showing that the particularly intense arteriosclerosis of the Mönckeberg type, the cardiac changes, and the nephrocalcinosis that were normally elicited in these animals with small doses of dihydrotachysterol when they were sensitized with monosodium phosphate could be inhibited by the concurrent administration of magnesium chloride or potassium chloride.

SAGALL

Lautsch, E. V., McMillan, G. C., and Duff, G. L.: Atherosclerosis in Rabbits after Intravenous Injection of Colloidal Solutions. Arch. Path. **65**: 40 (Jan.), 1958.

To check the effect on the serum lipids of the blocking of the reticuloendothelial system, New Zealand white rabbits were injected with colloidal thorium dioxide or methyl cellulose. Nine rabbits were given a single injection of colloidal thorium dioxide (3 ml. per Kg.) and a daily ration of 1 Gm. of cholesterol with 6 Gm. of corn oil. A second group of 9 rabbits received only the oral cholesterol and corn oil. A third group of rabbits was given an injection of colloidal thorium but no supplementary cholesterol or corn oil was given. The fourth group of rabbits was fed ordinary rabbit food. Rabbit pellets to supplement the daily diet intake were given to all 4 groups. There was a marked rise in total serum cholesterol, serum lipid phosphorus, and total fatty acids in the rabbits receiving colloidal thorotrast and cholesterol. There was an equal but less sharp rise in serum lipids in the rabbits getting the oral cholesterol. In the rabbits receiving the intravenous thorotrast there was only an evanescent rise to normal serum lipid levels by the third or fourth day. There was no change in serum lipid levels in the rabbits receiving only the daily ration of rabbit pellets. The control rabbits on ordinary food showed no atherosclerotic lesions of the aorta. Five of the 9 rabbits given colloidal thorium dioxide showed atherosclerotic lesions. The aortas of 8 of the 9 rabbits fed cholesterol and oil had atherosclerotic lesions. Seven of the 9 rabbits fed cholesterol and oil together with colloidal thorium dioxide showed atherosclerotic lesions. Particles of colloidal thorium dioxide were also noted within macrophages in the atherosclerotic lesions. Two of 10 rabbits fed ordinary food without added lipids and given intravenous injections of methyl cellulose showed prominent but transient hyperlipemia. One rabbit showed only a mild transient increase in concentration of serum lipids. The aortas of the 3 rabbits affected had small atherosclerotic lesions in the aorta. In the third part of this experiment, 6 rabbits were fed an ordinary diet and were given intravenous injections of colloidal thorium dioxide at semi-weekly intervals for many weeks. To the initial injection of thorotrast there was a marked hyperlipemic effect. Subsequent injections of thorotrast at 4 to 5-day intervals resulted in markedly less hyperlipemia with return of serum lipids to normal levels prior to each injection. The aortas of all the rabbits showed focal atherosclerotic lesions.

MAXWELL

Dayton, S.: Influence of Gallogen and Diethanolamine Upon Induced Hypercholesterolemia in the Rat. Circulation Research **6**: 271 (May), 1958.

Although Gallogen has been shown partly to prevent hypercholesterolemia in cockerels, it exaggerated the induced hypercholesteremia of rats. Diethanolamine, a constituent of Gallogen, had the same effect suggesting that this moiety was responsible for all the effects of Gallogen. It is speculated that the enhancement of elevated plasma lipid levels by these compounds is related to an antimetabolic effect of a diethanolamine-containing phospholipid.

AVIADO

Rivin, A. U., Yoshino, J., Shickman, M., Schjeide, O. A.: Serum Cholesterol Measurement—Hazards in Clinical Interpretation. J.A.M.A. **166**: 2108 (Apr. 26), 1958.

Conclusions drawn from determinations of total serum cholesterol must take into account the varying results of different laboratories, the discrepancies expected between samples taken on the same day, and the physiologic variations in a given individual over weeks or months. Duplicate serums from 3 patients with postmyocardial infarction were analyzed in 5 laboratories, 1 of which used 2 methods. There was a wide discrepancy in results. The physician should know the performance of the laboratory he selects and the laboratory's standard deviations of reproducibility. To be significant, a cholesterol level checked 1 time after therapy must decrease about 100 mg. per cent or there must be a decrease of about 60 mg. per cent that is consistently maintained. The appraisal of agents to lower serum cholesterol should be made with this data in mind.

KITCHELL

Wexler, B. C., and Miller, B. F.: Severe Arteriosclerosis and Other Diseases in the Rat Produced by Corticotrophin. Science **127**: 590 (March 14), 1958.

Both male and female rats, approximately 1 year old, were injected with corticotrophin (ACTH) 3 times a week for periods up to 7 weeks. The dose was 0.333 of a unit per 100 Gm. of body weight subcutaneously. The animals were fed a standard diet without additional fat or salt supplements. In female rats a fulminating type of arteriosclerosis involving the entire aortic tree was noted. A senile type of ectasia was present in the aorta and other large arteries. Arteriosclerotic changes extended into the cerebral, peripheral, and coronary vessels. Localized areas showed intimal swelling and proliferation, accompanied by medial hypertrophy and elasti tissue alteration. In some areas the media ad jacent to those with intimal proliferation showe necrosis and calcification. Intimal plaques con tained minute droplets of intracellular, and som extracellular fat. Special stains revealed change in the mucopolysaccharides of all arterial layer The coronary arteries were kinked and stiffene and showed intimal calcification, medial swellin and fragmentation of elastic tissue. Multipl infarctions were present in the ventricular por tion of the heart. Entirely different lesions wer found in male animals. About 30 per cent o them showed polyarteritis nodosa with sever aneurysmal dilatation, especially in the mesen teric vessels. Most of the animals showed unusu ally hard and firm testes, and about one third o the animals developed multiple renal calculi Unusually rapid aging, evidenced by lethargi behavior and worn condition of the coat, was seen in both older male and female rats.

WAIFE

BLOOD COAGULATION AND THROMBOEMBOLISM

Bobek, K., and Cepelák, V.: Laboratory Diagnosis of Venous Thrombosis. Acta med. scandinav. **160**: 121 (March 7), 1958.

The clot retraction time, the silicone tube coagulation time, and the platelet adhesiveness were studied for their suitability as laboratory methods for diagnosing venous thrombosis. When these 3 tests were performed on a group of healthy individuals and a group of patients with active venous thrombosis, the adhesive index provided the most clear-cut differentiation between the 2 groups of patients and had the highest index of diagnostic reliability. Similar results attesting to the superiority of the adhesive index were also obtained in the differential diagnosis between active venous thrombosis and other pathologic and predisposing states such as occur in patients with heart failure and malignancy and in the postoperative state. The adhesive index is also more elevated in acute thrombosis than in older or treated but still active thrombosis. Pronounced differences between recent and older stages of thrombosis were also found in the silicone tube coagulation times.

BROTHERS

Odegaard, A. E.: Permanent Anticoagulant Therapy—Complications and Rate of Mortality. Acta med. scandinav. **160**: 105 (March 7), 1958.

Two hundred and eighteen patients treated with a phenylindanedione preparation, Trombantin, for periods at least exceeding 2 months and in

some instances longer than 5 years, were subjected to follow-up examination with a view to complications and mortality rate. This group of patients represents a total period of 591 patient treatment years. In the group of patients with angina pectoris or myocardial infarction 17 died during the observation period yielding an average mortality rate of 5 per cent annually. In the group with obliterative arteriosclerosis of the lower limbs the average rate of mortality per year was 4 per cent. Twelve patients with mitral stenosis were treated for an average period of 3 years. Nine had atrial fibrillation and before treatment was started 6 episodes of embolism had occurred in 3 of the patients. During the treatment period no embolism occurred and there were no deaths. Exanthema occurred in 6 patients but disappeared upon discontinuing the drug. Neither agranulocytosis nor thrombocytopenia was observed. Hemorrhagic complications numbered 17 and included major epistaxis 2, hematuria 4, melena 9, hemothysis 1, and cerebral hemorrhage 1. The cerebral hemorrhage, which occurred in a patient with a brain tumor, proved to be fatal.

BROTHERS

Baer, S., Yarrow, M. W., Kravitz, C., and Markson, V.: Clinical Experiences with Warfarin (Coumadin) Sodium as an Anticoagulant. J.A.M.A. **167:** 704 (June 7), 1958.

Hypoprothrombinemic properties of warfarin (Coumadin) sodium and bishydroxycoumarin (Dicumarol) were evaluated in 200 patients. In 135 patients receiving warfarin, 65 per cent showed therapeutic effects in 24 hours or less, and 94 per cent exhibited beginning therapeutic effects in 42 hours. True therapeutic effects (prothrombin levels of 15 to 30 per cent) were reached by 87 per cent in 48 hours. One hundred and thirty-two patients (83.5 per cent) receiving warfarin were within therapeutic range 70 per cent of the time or more. With bishydroxycoumarin only 33.3 per cent of patients were within therapeutic ranges at least 70 per cent of the period of observation. The drug was easy to use and prothrombin times were controlled with small daily maintenance doses. There were no serious side effects and the 9 patients who showed bleeding phenomena responded promptly to whole blood and vitamin K or K_1 oxide. Warfarin seemed far superior to bishydroxycoumarin as an anticoagulant.

KITCHELL

Rosenberg, N., and Zullo, R. J.: Massive Venous Thrombosis Associated with Incoagulability of the Blood. Arch. Surg. **76:** 981 (June), 1958.

A 79-year-old man with right iliofemoral thrombophlebitis developed recrudescence of all symptoms after an initially good response to intermittent heparin therapy. Heparin, which had been decreased was resumed in increased amounts. On the tenth hospital day the blood remained incoagulable in all tubes after 2 hours. Clotting still failed to occur 36 hours after heparin was discontinued. A platelet count was 4000 per $mm.^3$ and 18 hours later was 2000. Following 3, fresh, whole-blood transfusions, ligation of the inferior vena cava was attempted because of pulmonary embolism. At surgery a thrombosed inferior vena cava was seen throughout the extent of the operative field with involvement also of the iliac veins. Thrombectomy was thought to be too hazardous in view of the extent of the thrombosis and the wound was closed. Heparin therapy was resumed cautiously after surgery with clotting times ranging from 7 to 22 minutes. However, the patient died in shock 2 days after operation. Postmortem examination disclosed a 2000-ml. retroperitoneal hemorrhage and complete occlusion of the iliac veins and inferior vena cava by a firm adherent thrombus, the upper end of which seemed to float freely in the lumen at the level of the renal veins with loose attachment to the main thrombotic mass. There was also a pulmonary embolus. Microscopically the thrombus and the pulmonary embolus were composed mainly of agglutinated platelets. It is postulated that there was exhaustion of the coagulation factors of the circulating blood by the extensive thrombotic process. Attention is also given to the possible etiologic significance of the so-called "heparin rebound" phenomenon, a period of hypercoagulability of the blood said to follow the abrupt cessation of heparin therapy or diminution in dosage.

BROTHERS

Silbert, S. and Zazeela, H.: Prognosis in Arteriosclerotic Peripheral Vascular Disease. J.A.M.A. **166:** 1816 (Apr. 12), 1958.

Observations of the course of peripheral vascular disease were made in 1,198 patients who satisfied certain criteria. Life expectancy in the uncomplicated case was not shortened. Eleven per cent of these patients died within 10 years and 33 per cent within 15 years from the onset of the symptoms. Where the disease was complicated by diabetes, the prognosis was graver, as 38 per cent of diabetic patients died in 10 and 69 per cent died in 15 years from onset. Moderate hypertension had no effect, but severe hypertension had an unfavorable influence on life expectancy as also did continued use of tobacco. Diabetic patients required amputation 4 times as

often as did nondiabetic subjects, and amputation rates were higher in females than in males. Although the continued use of tobacco increased the percentage of amputation, the presence of hypertension did not.

KITCHELL

Toohey, M.: Comparison of Quick's, Owren's and Ware's Techniques for the Control of Anticoagulant Therapy. J. Clin. Path. **11**: 56 (Jan.), 1958.

In this report all 3 methods for determining prothrombin time were carried out on 800 test plasmas. It appeared that Owren's technic gave better results for the control of anticoagulant therapy for in-patients as opposed to out-patients on long-term therapy. This was because Owren's method reflects changes in the blood 24 or even more hours before Quick's method does. For this reason, the dosage of the anticoagulant drug can be titrated more rapidly and the correct maintenance dose more quickly determined. In the long run, Quick's method will reflect even the most minute change in the dosage of the anticoagulant drug, but it takes longer to do so. For rapid anticoagulant therapy, therefore, as an acute embolic episode, when it is essential to get and maintain the patient under adequate anticoagulant cover as rapidly as possible and where it is usually necessary to make rapid and big changes in the dose of the anticoagulant drug, Owren's method is definitely better than Quick's. For out-patient long-term therapy, however, where the question of urgency does not arise and where blood specimens are taken at intervals of several weeks or more, there is no evidence that Owren's method is superior to Quick's method. Methods are outlined for preparing active and potent thromboplastin for the Owren's method. Better results were obtained by the addition of heparin to the anticoagulant for collection of the blood specimen, because this presumably stabilizes the clotting factors for several hours by preventing the activation of proconvertin. Calcium oxalate precipitate does adsorb small amounts of prothrombin and proconvertin, so that it is best to use citrate heparin and not oxalate heparin to collect the blood specimens. It was considered that Owren's method was more convenient and slightly better than Ware and Stragnell's modification of Owren's technic.

MAXWELL

CONGENITAL ANOMALIES

Shanahan, W. R., Romney, S. L., and Currens, J. H.: Coarctation of the Aorta and Pregnancy. J.A.M.A. **167**: 275 (May 17), 1958.

When hypertension occurs during pregnancy or soon thereafter coarctation of the aorta should be suspected. The absence of toxemia and of fetal mortality due to this abnormality is impressive. Among 10 patients reported there were 24 successful pregnancies and of these one third had postpartum blood pressures higher than the levels recorded during pregnancy. Death is so rare during or immediately postpartum that cesarean section is not indicated and if plans are made to resect the coarctation they should be deferred until after delivery.

KITCHELL

Davidsen, H. G.: Pulmonary Hypertension and Incompetence with Holodiastolic Murmur in Atrial Septal Defect. Acta med. scandinav. **160**: 177 (March 17), 1958.

Five patients with atrial septal defect who developed pulmonary hypertension and pulmonary incompetence were studied. The latter was characterized by the presence of a loud first pulmonary sound and a loud, blowing, pulmonary, diastolic murmur heard throughout the entire diastolic period, i.e. a holodiastolic murmur. Special investigation of the relationship of the murmurs and heart sounds to the intracardiac pressures and the valvular dynamics were conducted. The author regards enlargement of the pulmonary orifice as a very common, if not constant, finding in patients with atrial septal defect accompanied by an increased pulmonary flow. This enlargement is commonly described as dilatation of the pulmonary artery, both in radiologic and anatomic reports. The author makes a sharp distinction between hypertrophy and dilatation of the pulmonary orifice. He reserves the term dilatation for the reversible (elastic) increment related to pressure. The term hypertrophy is reserved for the permanent increase in size that occurs when the annular orifice, the valvular apparatus, and the pulmonary artery are all increased on an equal scale. This latter phenomenon is the typical finding in atrial septal defect. Increased stroke volume or pulmonary artery hypertension (both common in atrial septal defect) will increase the likelihood of pulmonary incompetence. On the contrary, hypertrophy of the pulmonary artery tree and of the pulmonary valvular apparatus is to some extent a compensatory measure and will diminish the likelihood of pulmonary incompetence. The continuation of the diastolic murmur until the end of diastole is dependent on a high end-diastolic pressure, and may thus be regarded as a clinical sign indicating the presence of a very high pulmonary resistance.

BROTHERS

Devitt, R. E., and Pinto, C. J.: Congenital Heart Block due to Endocardial Fibroelastosis Interpreted as Foetal Distress. J. Obst. & Gynaec, Brit. Emp. **64**: 885 (Dec.), 1957.

A 6 pound, 9 ounce boy was delivered by cesarean section because of the finding of a slow fetal heart rate in early labor. The fetal heart was found to be irregular in rhythm, and its rate over 1 minute was 60. The baby otherwise appeared normal and remained well the first day, the apex rate varying from 40 to 100 per minute. An electrocardiogram taken on the second day showed complete atrioventricular dissociation. A chest x-ray showed enlargement of the heart but clear lungs. The baby became progressively more cyanotic and died on the fourth day. No history of maternal infection during preganancy was obtainable. The heart weighed 40 gm., and the pericardium was adherent over a small area on the anterior surface of the left ventricle. All chambers were dilated. Although both ventricles were involved, the fibroelastosis was more pronounced on the right side. There was no evidence of any gross septal defect to explain the congenital heart block.

MAXWELL

CONGESTIVE HEART FAILURE

Dresdale, D. T., Greene, M. S., and Guzman, S. P.: Clinical and Hemodynamic Effects of Cortisone in Patients with Rheumatic Heart Disease and Congestive Heart Failure. Am. Heart J. **55**: 851 (June), 1958.

Six patients with rheumatic heart disease (3 with mitral stenosis and 3 with mitral stenosis and insufficiency) and pulmonary congestion and right heart failure were observed while receiving a course of cortisone. Slight improvement in cardiovascular hemodynamics was found in 4 patients. In these patients there were decreases in pulmonary artery, pulmonary "wedge," or right ventricular end-diastolic pressures without significant changes in cardiac output. In 3 patients the plasma volumes decreased, in 2 symptomatic improvement in cardiac status occurred, and in 3, the body weights decreased. Two patients suffered a deterioration of their cardiovascular hemodynamics while on cortisone therapy, characterized by increases in pulmonary artery, pulmonary "wedge," or right ventricular end-diastolic pressures without any significant changes in cardiac output. In 1 of these 2 patients the plasma volume was found to be increased. Subjective improvement was noted in 1 patient and in both patients the body weight increased. The possible mechanisms whereby cortisone may have influenced the cardiovascular hemodynamics are discussed.

SAGALL

Gold, H., Greiner, T. H., Warshaw, L., Kwit, N. T., and Ganz, A.: Diuretic Action of Two Carbonic Anhydrase Inhibitors in Congestive Failure. J.A.M.A. **167**: 814 (June 14), 1958.

Two carbonic anhydrase inhibitors, acetazolamide (Diamox) and ethoxzolamide (Cardrase), were compared with intramuscularly given meralluride by oral administration in a group of ambulatory patients with congestive heart failure. The criterion of response was a 24-hour weight loss. The average maximum response with acetazolamide (oral) was obtained with 125 mg., and the average maximum diuretic effect was somewhat less than that obtained from 0.5 mg. of intramuscularly given meralluride. Increasing from a daily dose of 125 mg. of acetazolamide (even 8 times as much) did not increase the response. It was found that when oral acetazolamide (125 mg.) was given with intramuscular meralluride the response was that expected from merulluride alone. The average maximally effective oral dose of ethoxzolamide produced a greater diuretic response than acetazolamide and was equivalent to approximately 0.7 ml. of intramuscularly given meralluride.

KITCHELL

Holger-Madsen, T.: Heparin Tolerance Test during Dehydration of Patients with Congestive Heart Failure. Acta med. scandinav. **160**: 109 (March 7), 1958.

Is the risk of thrombosis and embolism increased during dehydration of patients with cardiac decompensation? In seeking an answer to this question, the coagulability of the blood was studied, by means of the heparin tolerance test, in 22 patients with decompensated heart disease treated with mercurial diuretics, low salt diet, digitalis, purine derivatives, and in most instances ammonium chloride. During treatment, half the patients demonstrated hypercoagulability in the form of definite shortening of the clotting time, i.e. a shortening of 20 per cent or more compared with the pretreatment value. In 2 patients the shortening occurred before and in 9 after the treatment with mercurials was started. Shortening of the clotting time was not apparent in any of 20 tests 3 to 6 hours after a mercurial injection, which militates against a direct pharmacologic effect of mercurial diuretics on the clotting process. Whether or not the hypercoagulability is caused by the dehydration proper, it appears during dehydration. According to this study, however, it does not seem likely that this hypercoagulability is due exclusively to the dehydration, as no correlation was found between the hypercoagulability and the intensity of dehydration, assessed on the basis of the urinary output

and of the effect of treatment on the objective signs of congestive heart failure. Hypercoagulability was apparently not influenced by whether or not the patients had been bedridden or ambulatory from admission. Neither did the duration of bed rest have any influence on the occurrence of hypercoagulability. Only 1 thromboembolic complication occurred in this series and that was in an individual in whom clotting of the blood was classified as being doubtfully shortened.

BROTHERS

Kako, K., and Bing, R. J.: Contractility of Actomyosin Bands Prepared from Normal and Failing Human Hearts. J. Clin. Invest. **37**: 465 (March), 1958.

By a special technic bands of actomyosin prepared from heart muscle of dogs were found to have undiminished contractility for 1 hour post mortem. In this study, material was obtained at autopsy from 41 human hearts at periods of from 1 to 6 hours after death. Twelve patients had died from congestive heart failure due to arteriosclerotic or hypertensive heart disease; the remainder died from various medical illnesses. It was found that the contractility of these bands remained undiminished for at least 6 hours after death. Actomyosin bands from normal hearts showed a reverse relationship between load and percentage shortening. Nicotine caused a slight diminution in the contractility of the band. Calcium chloride and digoxin when added separately had no effect. However, when calcium and digoxin were combined, the shortening of the bands was increased. There was a significant diminution in the contractility of the actomyosin bands prepared from human hearts following congestive failure. Digoxin failed to correct this defect. The combination of digoxin and calcium chloride restored shortening of the bands to normal. These results, although confirming the existence of changes in actomyosin of failing hearts, permit no conclusion on the nature of these alterations.

WAIFE

CORONARY ARTERY DISEASE

Von F. Kubicek-Wien: Course and Prognosis of Rudimentary Anterior Wall Infarction. Cardiologia **32**: 257, 1958.

The term, rudimentary anterior wall infarction was introduced by Holzmann for a particular variety of myocardial infarction characterized by a typical history, development of ischemic T-wave alterations (without QRS changes) in the precordial leads and a benign clinical course. The author presents an analysis of the clinical features of 35 such patients. Eleven additional ones are mentioned in an addendum; 1 of the latter died from uremia due to polycystic kidneys, and autopsy revealed partial occlusion of the left coronary artery with a small intramural myocardial infarction. All other patients recovered, but 11 developed a typical transmural infarct usually within 2 to 3 months. In view of this high recurrence rate, the author recommends caution in prognosis and institution of long-term anticoagulant therapy after the initial episode. Difficulties in the differential diagnosis of the initial electrocardiographic alterations are emphasized.

PICK

Thomas, C. B.: Familial and Epidemiologic Aspects of Coronary Diseases and Hypertension. J. Chron. Dis. **7**: 198 (March), 1958.

A study was made of 724 Johns Hopkins medical students correlating the incidence of hypertensive disease and coronary artery disease in the parents of these subjects with the manifestation of elevated or labile blood pressure, elevated heart rate, circulatory hyperactivity, and overweight in the subjects. In general, a higher more labile blood pressure and heart rate and a higher incidence of overweight were found among students with a positive parental history of hypertension. Although the difference between the 2 groups as to incidence of single traits was often not great, about 40 per cent of the offspring of hypertensive parents had multiple positive traits, 2½ times as many as were found among the offspring of normal parents. Hypercholesteremia or cholesterol levels of 300 mg. per cent or more, on at least 1 occasion was much more frequent among the offspring of parents with coronary disease than among those with normal parents. In the entire group of hypercholesteremic students, 32 per cent had a parent with coronary disease in contrast to 12 per cent of those with normal cholesterol values. A study of the smoking habits of the students showed that the incidence of parental hypertension and coronary disease was higher among subjects who were regular smokers than among subjects who were nonsmokers or only occasional smokers. There was no statistically significant correlation between the incidence of smoking in the subjects and the history of parental coronary heart disease, however. The observation was also made that at the 3 lower blood cholesterol levels among the students, i.e., under 250 mg. per cent smokers were in the minority, whereas at higher levels, i.e., 250 mg. per cent or more, the smokers predominated. This was especially true for the 48 hypercholesteremic subjects, 62.5 per cent of whom were

smokers. The hypercholesteremic subjects all had serum cholesterol values above 300 mg. per cent.

MAXWELL

Marcus, E., Katz, L. N., Pick, R., and Stamler, J.: The Production of Myocardial Infarction, Chronic Coronary Insufficiency and Chronic Coronary Heart Disease in the Dog. Acta cardiol. **13**: 190, 1958.

A surgical procedure is described for the production in dogs of chronic heart disease by multiple coronary embolization with plastic beads, resulting in congestive heart failure, ascites, and peripheral edema. Pathologic findings consisted of myocardial infarction, fibrosis, dilatation of the heart, and aneurysm formation resembling features of the human disease. Limb-lead electrocardiograms did not always reveal anatomically demonstrable myocardial changes. Complete sets of precordial leads (V_1-V_6) showed signs of infarction in the early postoperative period, but were not characteristic in chronic animals. Dogs with experimentally produced chronic coronary heart disease are useful for the study of revascularization procedures as well as of the dynamics of myocardial failure.

PICK

Sabiston, D. C., Jr., and Blalock, A.: Experimental Ligation of the Internal Mammary Artery and Its Effect on Coronary Occlusion. Surgery **43**: 906 (June), 1958.

The volume of blood flow in the internal mammary artery was determined in dogs following experimental ligation of this vessel in the second intercostal space. The flow was measured immediately after ligation in some experiments and after an interval of weeks in others. The volume of flow was found to be quite small in both groups of experiments with correspondingly low values for backpressure and backflow. Small arterial communications between the internal mammary branches and the perivascular arteries along the great vessels entering the heart could be demonstrated by injection technics, although no protection of the heart against deliberate ligature of the anterior descending coronary artery was found. Blood flow in the internal mammary artery was significantly increased in the chronic preparation in those experiments in which concomitant ligation of the remaining branches of the subclavian artery was performed. Despite the increase in flow, backpressure and backflow consistently observed under these circumstances, no protection appeared to be offered the heart when challenged by ligation of the anterior descending coronary artery. It is concluded from these studies that the volume of blood flowing through the internal mammary artery following ligation in the second intercostal space is quite small and that the procedure does not protect against experimental coronary occlusion.

BROTHERS

White, P. D., Bland, E. F., and Levine, S. A.: Further Observations Concerning the Prognosis of Myocardial Infarction Due to Coronary Thrombosis. Ann. Int. Med. **48**: 39 (Jan.), 1958.

As emphasized in 1941 and 1956, the most important clue favoring longevity and a return to a normal program of life was found to be the degree of completeness of recovery after the first month of convalescence from the acute attack of myocardial infarction. Of the 24 patients who showed neither myocardial nor coronary insufficiency, 18 (75 per cent) survived 5 years while the average survival of these 24 patients was 12 years. Of 25 patients who died within 3 years of the onset of their attack, 14 had congestive heart failure (6 had coronary insufficiency also), 7 had angina pectoris without congestive failure, and only 4 were free from evidence of either complication during their convalescence after the first month. Among 23 who survived 5 years, only 1 had congestive failure, 4 others had angina pectoris, and 18 had recovered completely from their acute attack showing neither complication. There was a steadily decreasing mortality during the first 3 months. Of 35 who died in the first month, 18 died in the first week and 8 in the second week. Of the 42 who died in the first 3 months, 26 succumbed in the first fortnight, 9 more in the second fortnight, and only 7 others in the second and third months.

WENDKOS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY AND OTHER GRAPHIC TECHNICS

Morton, W., Lloyd, L., Dodge, H. J., and Hoffman, M. S.: Use of a Single-lead ECG in the Detection of Congenital Heart Disease. J. Dis. Child. **95**: 492 (May), 1958.

A study of 1,846 school children from a community in Colorado with a population of 12,000 was undertaken in order to investigate the hypothesis that a single-lead electrocardiogram showing a pattern of right ventricular hypertrophy would serve as a screening mechanism to pick up any congenital heart disease that resulted in right ventricular hypertrophy. It was hoped that this screening would pick up cases of atrial septal defect, pulmonic stenosis, tetralogy of Fallot, and patent ductus arteriosis with reverse

shunt, and varieties of ventricular septal defect resulting in right ventricular hypertrophy. The V_3R lead was chosen, and the criteria for abnormality were that the ratio of the R wave to the S wave was greater than one, that the prolongation of ventricular activation time was 0.04 second or longer, and that there was a prominent "crista" pattern, which is an increased prominence of the R-prime wave in the r-S-r prime complex. The single-lead electrocardiogram was recorded by the school nurse, followed up by physical examinations done by teams of pedintricians. Forty-seven children were selected as having either heart disease or needing evaluation before heart disease could be ruled out, and these were checked by a pediatric cardiologist who verified 17 cases of organic heart disease. From the single-lead electrocardiogram there were 19 abnormal tracings which produced a yield of 5 children who on complete examination had congenital heart disease. There were 14 false positives in the abnormal group, giving a specificity of 26 per cent and there was 1 false negative in the normal group, giving a specificity of 83 per cent, which yields an index of efficiency of only 21.6 per cent. When the "crista" pattern was omitted from the evaluation of the electrocardiographic findings there was a specificity of 35 per cent in the false positives and 83 per cent in the false negatives, giving an index of efficiency of 29 per cent. The authors believe that this screening procedure or modifications of it should be tested further to see if the statistical validity and efficiency can be increased.

HARVEY

Cayler, G. G., Ongley, P., and Nadas, A. S.: Relation of Systolic Pressure in the Right Ventricle to the Electrocardiogram: A study of Patients with Pulmonary Stenosis and Intact Ventricular Septum. New England J. M. **258:** 979 (May) 1958.

The electrocardiogram was studied in 105 patients who were proved to have pulmonary stenosis with intact ventricular septum by cardiac catheterization. Analysis of the data showed that, although the pressure in the right ventricle could not be accurately predicted from the ratio of pressure to voltage of R in V_1, there was a good correlation for the regression equation of 3 times the voltage plus 47. It was further noted that when the R wave in V_1 was 20 mm. or greater the systolic pressure in the right ventricle was almost always at least 100 mm. Hg whereas with an R wave of less than 20 mm. the right ventricular systolic pressure was rarely above 100 mm. Hg. Patients with right ventricular pressures of 100 mm. Hg or higher almost always had either an R wave in lead V_1 of 20 mm. or taller or a pure R or qR wave in lead V_1 or both. Such findings were not seen in patients with pressures in the right ventricle of less than 70 mm. with the exception of 3 patients seen after pulmonary valvotomy. When the pressure was 150 mm. Hg or higher there were almost always S-T segment and T-wave changes in V_1 as well as tall R waves. Conversely, patients with an R wave in lead V_1 of 20 mm. or more plus S-T segment and T-wave changes usually were found to have systolic pressures in the right ventricle greater than 150 mm. Hg and never below 100 mm.

SAGALL

Zimmerman, H. A., de Oliveira, J. M., Nogueira, C., Mendelsohn, D., and Kay, E. B.: The Electrocardiogram in Open Heart Surgery. J. Thoracic Surg. **36:** 12 (July), 1958.

The authors studied disturbances in right ventricular conduction in 63 patients who had undergone open heart surgery. In 21 patients there were no alterations in right ventricular conduction. In the remainder, the changes were classed as first degree (appearance of R′ or R′S′ in lead V_1, but without significant prolongation of QRS), or second degree (R′ or R′S′ in V_1 with wide S_1 and wide R_{aVR}, plus widening of QRS).

In atrial septal defects (15 patients) there were no first- or second-degree changes. In valvular pulmonic stenosis (13 patients) there were no second-degree changes and 8 instances of first-degree alterations. Second-degree changes were found in all patients in whom resection of the pulmonary infundibulum was performed (17 patients) of infundibular stenosis or tetralogy of Fallot) and in 10 of 18 patients with ventricular septal defect. The implication is that there is an area in the right ventricle that is always damaged during infundibular resection and frequently during closure of ventricular defects. The electrocardiographic changes have persisted even a year after operation. Experimental evidence is presented which indicates that patterns of right bundle-branch block may result not only from direct damage of the right branch itself but also from injury to the crista supraventricularis and the surrounding region. There is no evidence to suggest that these conduction disturbances were responsible for the higher mortality in the cases of pure and associated infundibular stenosis.

ENSELBERG

Gross, D.: Breath-Holding as Anoxemia Test. Cardiologia **32:** 302, 1958.

Voluntary breath holding may cause electrocardiographic changes of the anoxemic type. This provides an opportunity for verification of sus-

pected angina by a simple test suitable for office practice. The electrocardiogram is registered in lead II, a few seconds prior to the previously determined maximal breath holding time. A positive result is indicated by inversion of the T wave or marked displacement of the S-T segment. The author found such changes in 53 per cent of patients with evident or suspected anginal pain. On the other hand, "false" positive reactions were observed in 15 per cent of cases with normal electrocardiograms. On the basis of these data, it is concluded that "a positive breath holding test indicates an anoxemic myocardial disturbance caused most frequently by coronary insufficiency; a negative test excludes neither coronary disorders nor affirms normality."

PICK

Hale, D. E., and Moraca, P. P.: Electrocardiogram and Electroencephalogram in Elective Cardiac Arrest. J.A.M.A. **166:** 1672 (April 5), 1958.

Continuous electrocardiographic and electroencephalographic monitoring is especially valuable during cardiac surgery. The electrocardiogram reveals cardiac arrhythmias but gives little evidence of anoxia and hypercapnia. In cardiac arrest, when most of the signs of anesthesia fail and the electrocardiogram is a flat line, the electroencephalogram is useful as an indicator of cerebral oxygenation. Depression of cortical output results from hypotension, decreased blood flow, hypothermia, cerebral anoxia, anesthesia, hypercarbia, and stimulation of the carotid body. Both the electrocardiogram and the electroencephalogram help to main close rapport between the anesthetist and the physiologic state of the patient.

KITCHELL

Sloan, A. W.: The Clinical Significance of Cardiac Gallop Rhythm. Am. Heart J. **55:** 715 (May), 1958.

Phonocardiographic study of 100 hospitalized patients with heart disease disclosed protodiastolic (third sound) gallop rhythm in 15, presystolic gallop rhythm in 10 and train-wheel rhythm (third and fourth sounds) in 4. Protodiastolic gallop was found to be associated with right heart strain and presystolic gallop and train-wheel rhythm with left heart strain or myocardial damage. These phenomena were not related to the age, sex, or heart rate of the patients or to the presence of cardiac failure. In the entire series, patients with a fourth heart sound (presystolic gallop or train-wheel) rhythm showed significant deterioration relative to the other patients after 6 to 9 months. Of the patients with mitral stenosis and aortic incompetence only those with protodiastolic gallop rhythm showed significant deterioration. After 25 to 34 months no significant correlation was found between the patient's condition and the presence or absence of gallop or train-wheel rhythm at the original study. The authors conclude that the findings of this study show that gallop rhythm is not of such grave prognostic significance as has been believed in the past.

SAGALL

Sodi-Pallares, D., Pileggi, F., Cisneros, F., Ginefra, P., Portillo, B., Medrano, G. S., and Bisteni, A.: The Mean Manifest Electrical Axis of the Ventricular Activation Process (AQRS) in Congenital Heart Disease: A new Approach in Electrocardiographic Diagnosis. Am. Heart J. **55:** 681 (May), 1958.

The authors point out the value of determining the mean manifest electric axis of the ventricular activation process in the diagnosis of congenital heart disease. Tables of the distribution of frequency of the main forms of cyanotic and acyanotic congenital malformations in each of the sextants of the triaxial systems are presented. Each sextant is then studied and elaborated upon separately. Several examples illustrating this approach to the interpretation of electrocardiographic tracings in cases of congenital heart disease are discussed.

SAGALL

August, T., Mazzeleni, A., and Wolff, L.: Positional and Respiratory Changes in Precordial Lead Patterns Simulating Acute Myocardial Infarction. Am. Heart J. **55:** 706 (May), 1958.

Three patients are presented in whom precordial lead QRS changes produced by respiration or slight shift in the position of the exploring electrodes simulated those seen in acute myocardial infarction. It is believed that such changes depend upon the position and nearness of the exploring electrode in relation to the electric center of ventricular depolarization. These cases illustrate the need for caution in interpreting serial changes in the precordial leads of the electrocardiogram, particularly when they are seen in or near the transitional zone.

SAGALL

Scher, A. M., Liikane, J., Rodriguez, M. I., and Young, A. C.: "Slow" Potential Change in the Atrioventricular Node. Science **127:** 873 (April 18), 1958.

Small electrodes were placed in the atrioventricular node of the perfused isolated heart of dogs. Study of the potentials led to the follow-

ing description of A-V nodal conduction: atrial cells in the A-V nodal region trigger atrionodal cells. These differ histologically from both atrial and nodal cells. These cells activate the nodal cells, and a slow potential change propagates through the A-V node. The slow potential in turn depolarizes the bundle.

WAIFE

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Sayers, E. G.: Diphtheritic Myocarditis with Permanent Heart Damage. Ann. Int. Med. **48**: 146 (Jan.), 1958.

An outstanding British athlete developed diphtheria while assigned to military service in Egypt in 1942. At that time he was 29 years old. Electrocardiographic studies during the acute infection revealed changes compatible with myocardial disease. He apparently made a good recovery and between 1946 and 1954 remained in good health and retained his enthusiasm for all sports and participated in cricket matches and played badminton. In September 1954 he was found to be suffering from congestive heart failure. At that time x-ray studies demonstrated enlargement of the heart and the electrocardiogram revealed changes interpreted to be those of a previous anterior infarction. He never fully recovered from his congestive failure and x-ray studies demonstrated progressive enlargement of the heart. He developed a protodiastolic gallop rhythm and frequent premature beats. In spite of the usual measures for the treatment of congestive failure, including anticoagulant therapy because of a phlebothrombosis and pulmonary infarction, his condition deteriorated rapidly and he died on December 24, 1954. Autopsy revealed the presence of diffuse fibrosis throughout the myocardium without any associated coronary arteriosclerosis. It was considered that the myocardial fibrosis was a sequel to the attack of diphtheria. This case therefore represents one of those rare instances of death resulting from previous diphtheritic myocarditis, leading eventually to diffuse myocardial fibrosis and congestive heart failure.

WENDKOS

Robinson, R. W., Cohen, H. D., and Higano, N.: Estrogen Replacement Therapy in Women with Coronary Atherosclerosis. Ann. Int. Med. **48**: 95 (Jan.), 1958.

Significant differences of serum lipid patterns have been demonstrated in normal women of various ages. The serum lipid patterns observed in women with coronary heart disease were not significantly different from those of clinically normal postmenopausal women, save for an increased beta-alpha-lipoprotein-cholesterol ratio. Previously hysterectomized women with coronary heart disease were treated with a high dosage (5 or 10 mg.) of Premarin daily for from 2 to 31 months. There was a dramatic serum lipid response as early as 1 month, with a reduction of the cholesterol-phospholipid and beta-alpha-lipoprotein-cholesterol ratios to levels comparable to those of normal young women within 3 months. A low-dosage schedule revealed that 1.25 mg. of Premarin daily adequately reduced the cholesterol-phospholipid and beta-alpha-lipoprotein-cholesterol ratios in women whose ratios were initially below the group mean. In women with ratios initially above the group mean, this dosage failed to achieve a comparable level. An increase of dosage to 2.5 mg. daily resulted in a satisfactory lowering of the cholesterol-phospholipid ratio, although the beta-alpha-lipoprotein ratio remained somewhat elevated. Complications of estrogen therapy have been noted, but these were not serious. They included breast tenderness, recurrence of migraine, and nocturnal cramps of the leg muscle. Breast tenderness was temporary, but either migraine leg cramps, when sufficiently severe, made necessary the cessation or decrease of estrogen dosage.

WENDKOS

Movitt, E. R., Lennette, E. H., Mangum, J. F., Berk, M., and Bowman, M. S.: Acute Benign Pericarditis: Report of Two Cases Associated with Group A and Group B Coxsackie Viruses. New England J. Med. **258**: 1082 (May 29), 1958.

Two cases of acute benign pericarditis are reported in whom there was evidence incriminating the Coxsackie viruses as the causal agent. In 1 case a Coxsackie virus identified as group B, type 3, was recovered from the stool and there was a rise in the serum neutralizing antibody against this virus. In the other patient a Coxsackie virus, group A, type 1, was found in a similar manner. The authors suggest that the clinical state generally recognized as "benign," "idiopathic," or "nonspecific" pericarditis should be considered as a syndrome rather than as an etiologic entity, since in some cases the Coxsackie group of viruses may be the causative organism.

SAGALL

Hoel, J.: Reappearance of Complete Heart Block Years after Diphtheritic Myocardial Disease. Acta med. scandinav. **160**: 237 (March 17), 1958.

Diphtheritic heart disease is accompanied by a significant mortality, but once the acute stage is

overcome, usually no significant heart damage is demonstrable. In rare instances, however, relapse of a heart block, first appearing during the acute phase, may occur up to several years after the acute illness. Two such instances are reported. Both patients had severe diphtheritic myocardial disease affecting the conducting system of the heart during the acute attack of diphtheria. After the acute phase of the illness was over no signs of cardiac disease were apparent. However, 1 patient, after 6 years of good health, experienced fainting episodes, probably Stokes-Adams attacks. Eleven years after the onset of diphtheria she had a variable heart block changing between partial and complete. The second patient, 3 years after the diphtheria, became subject to dizziness and syncopal episodes. An electrocardiogram disclosed atrioventricular block. One year later he had recurrence of the same trouble. Following this he had no further subjective symptoms of heart disorder but electrocardiograms taken 8 and 14 years after the diphtheria revealed complete heart block. The late reappearance of heart block in these patients is believed to be due to changes taking place in small fibrotic areas in the conduction system, the fibrosis having occurred at the time of the acute diphtheritic process.

BROTHERS

HYPERTENSION

Maxwell, R. A., Plummer, A. J., Ross, S. D., and Daniel, A.: Studies concerning the Cardiovascular Actions of the Central Nervous Stimulant, Methylphenidate. J. Pharmacol. & Exper. Therap. **123**: 22 (May), 1958.

This study deals with the nature and sites of the cardiovascular actions of methylphenidate. High doses produced a sharp, very transient fall in blood pressure but no marked, sustained depressor effects. The same dose restored the blood pressure to control levels in a dog with amphetamine-induced hypertension. This action of methylphenidate against amphetamine hypertension appeared to be specifically antihypertensive and not the result of a general hypotensive action. This blocking effect of methylphenidate also had a distinct peripheral component. Five and 10 mg. per Kg. doses of methylphenidate, intravenously, markedly reduced the pressor response elicited by bilateral common carotid artery occlusion in the intact dog while not markedly lowering the blood pressure. This effect could not be explained by an obvious afferent or efferent peripheral blockade. Finally, determinations of the effect of methylphenidate on renin hypertension indicated that the moderate antihypertensive effect of methylphenidate in the renal hypertensive dog could not be explained by a blocking effect on the renin pressor system.

RINZLER

Wilkins, R. W.: Precautions In Use of Antihypertensive Drugs, Including Chlorothiazide. J.A.M.A. **167**: 801 (June 14), 1958.

Antihypertensive therapy should lower blood pressure gradually by using the safest, mildest, and least symptom-producing drugs, and dosages should be regulated by patient observation over weeks or months. Proceeding from the milder to the stronger antihypertensive drugs, one may try successively and in combination Rauwolfia, Veratrum, hydralazine, chlorothiazide, and a ganglionic-blocking agent. By using minimal effective doses in combination, a satisfactory regimen can usually be found that will lower the blood pressure reasonably. Changes in dosage should be made gradually. Repeated attempts should be made to reduce dosages or omit drugs if this can be done without a rise in blood pressure. Caution should always be used, especially with stronger drugs and long-term therapy. Each drug may be employed in combination with any other.

KITCHELL

Dahl, L. K., Silber, L., and Christie, R. W.: The Role of Salt in the Fall of Blood Pressure Accompanying Reduction in Obesity. New England J. Med. **258**: 1186 (June 12), 1958.

Observations are reported on 12 ambulatory adult patients with hypertension and obesity who were hospitalized on a metabolic ward and given combinations of low sodium and high or low calorie diets. The results obtained in this study suggest that in obese hypertensive patients reduction of weight uncommonly leads to reduction of blood pressure unless salt intake (in the form of sodium chloride) is also reduced. In only 1 patient in whom the original diagnosis of essential hypertension was questionable because of her gross obesity was weight reduction alone accompanied by a fall in blood pressure. On the basis of these findings the authors suggest that when a fall in blood pressure follows the institution of a weight-reduction program in obese hypertensive patients, the lowering of the blood pressure is due to the associated reduction of salt intake and not to the restriction of calories.

SAGALL

Tobian, L., Thompson, J., Twedt, R., and Janecek, J.: The Granulation of Juxtaglomerular Cells in Renal Hypertension, Desoxycorticosterone and Postdesoxycorticosterone Hypertension, Adrenal Regeneration Hypertension, and Adrenal Insufficiency. J. Clin. Invest. **37**: 660 (May), 1958.

Certain cells of the juxtaglomerular complex contain discrete secretory granules. These cells are in a position which could be particularly affected by changes in intraluminal pressure and such cells could be stretchers that change their rate of secretion in response to changes in stretch. In this study renal hypertension was produced in rats by renal arterial constriction. A special staining technic for the juxtaglomerular apparatus was used. A juxtaglomerular "index" was developed that indicates the degree of granulation of cells. The granules doubled in the ischemic kidney when there was partial constriction of 1 renal artery and hypertension. The granules virtually disappeared in the untouched contralateral kidney. When the ischemic kidney was excised several weeks later, hypertension disappeared and the granules reappeared in normal abundance in the previously completely degranulated "normal" kidney. Adrenalectomy doubled the juxtaglomerular index, but desoxycorticosterone and salt caused the granules to disappear while producing hypertension. Changes were also seen in the juxtoglomerular index in experiments with other forms of hypertension. In general, where the renal arterial bed was exposed to hypertensive pressures, granulation of the cells was decreased; conversely, when the blood pressure in the renal bed was lowered, the cells tended to increase in granulation. Since these cells did undergo marked changes in granulation in various forms of experimental hypertension, their exact role in these situations deserves further study.

WAIFE

Sturtevant, F. M.: Antihypertensive Effects of an Aldosterone Antagonist. Science **127**: 1393 (June), 1958.

A synthetic steroid (SC-5233) has been shown to antagonize the renal excretory effects of aldosterone and deoxycorsterone acetate in rats and man. This report is the result of a study on the effect of the compound to prevent and reverse experimental hypertension produced in rats by DCA (deoxycorticosterone acetate). Pellets of DCA were implanted in rats and salt was added to the drinking fluid. One group of animals received the steroid in doses of 10 mg. per Kg. per day subcutaneously for 19 days; the other served as control. Blood pressures taken periodically under "double-blind" conditions showed no differences between the blood pressure until about the fifteenth or eighteenth day. At that time the untreated group had a statistically significant higher blood pressure. Other studies reveal that the compound had a hypotensive action when administered both orally and parenterally in rats who were "metacorticoid hypertensive" and no longer under the active metabolic influence of DCA. It is postulated that the renal mineralocorticoid-blocking and the antihypertensive properties of this steroid are not directly related. The antihypertensive effect may be mediated by the reversal of a disturbance in internal electrolyte metabolism such as may have been instituted by the temporary treatment with DCA.

WAIFE

PATHOLOGY

Halpert, B., Erickson, E. E., DeBakey, M. E., Creech, O., Jr., and Cooley, D. A.: Occlusive Disease of the Abdominal Aorta. Structural Alterations. Arch. Path. **65**: 158 (Feb.), 1958.

The structural changes occurring in the abdominal aorta and common iliac arteries in occlusive disease were studied in 45 surgically removed specimens. The patients were all men, 43 white and 2 Negro. The ages ranged from 33 to 66 years with the majority of the patients being in the fifth and sixth decades. The occlusion of the aorta was clinically complete in 26 and incomplete in 19 cases. In all specimens the occlusive process was due to atherosclerotic changes in the walls of the aorta and common iliac arteries. Usually the atherosclerotic and calcific changes in the intima and media narrowed the lumina of the common iliac arteries up to one third of their original caliber. It was observed that a constant focal or diffuse chronic inflammatory reaction commenced in the common iliac arteries and decreased in severity and extent upward from the bifurcation of the aorta. It is suggested that the inflammatory process observed may have a part in precipitating the occlusion.

MAXWELL

Best, P. V., and Heath, D.: Pulmonary Thrombosis in Cyanotic Congenital Heart Disease without Pulmonary Hypertension. J. Path. & Bact. **75**: 281 (April), 1958.

In 7 patients with different types of cyanotic congenital heart disease without pulmonary hypertension who came to autopsy a systematic study of the incidence and distribution of pulmonary thromboses in vessels of the lungs was made. Blocks were taken from approximately the same areas in both upper and lower lobes in each lung, and the vessels, muscular pulmonary arteries, pulmonary veins and arterioles, and small veins were studied for types of intimal lesions. These lesions were classified as eccentric thrombotic lesions, concentric thrombotic lesions, age change, and lesions resembling recanalization. Two hundred vessels were counted and tabulated from each of 4 different sections in each case.

Two main groups of thrombotic lesions were present; namely, nodular eccentric and recanalized types of lesions with fibrin in abundant amount and eccentric, crecentric, concentric recanalized lesions without fibrin. It was thought that the changes of the concentric and crecentric thrombotic lesions are merely expressions of normal age change. The authors believe that many of the lesions referred to as recanalized types were actually the result of a division of the endothelium, for the eccentric nodular lesions occasionally met in the center of the vessel and the channels left were always in the periphery and lined by what appeared to be normal endothelium from the original vessel. Vessels were rarely totally occluded by thrombus. It was considered that the main etiologic factors concerned in these thromboses were the reduced rate of pulmonary blood flow and the increased viscosity from secondary polycythemia. These experiments confirm Rich's observations made earlier on this same type of lesion. The blood vessels in the lung in these cases also showed a very high development of collateral bronchial circulation.

HARVEY

PHARMACOLOGY

Hess, M. E., and Haugaard, N.: Studies of the Effect of Antiarrhythmic Drugs on Carbohydrate Metabolism of the Rat Heart Muscle in Vitro. Circulation Research **6**: 256 (May), 1958.

There is general agreement that a common property of the antiarrhythmic drugs now in clinical use is the ability to decrease the excitability of the myocardium. One possible way in which such an action could be brought about is prolongation of the recovery period of heart muscle by depressing energy-yielding reactions of carbohydrate metabolism. Quinidine strongly depressed the oxygen uptake and glucose utilization of rat heart slices and homogenates. In contrast, chloroquine had little effect and procaine amide had none. Depression of carbohydrate metabolism was therefore not essential for the action of antiarrhythmic drugs.

AVIADO

Gilbert, J. L., Lange, G., Polevoy, I., and McC Brooks, C.: Effects of Vasoconstrictor Agents on Cardiac Irritability. J. Pharmacol. & Exper. Therap. **123**: 9 (May), 1958.

The effects of the vasoconstrictor drugs epinephrine, levarterenol, methoxamine, and mephentermine were studied on excitability, refractory period, rhythmic abnormalities, conduction times, and action potential of the heart. When blood pressure levels were maintained 30 to 50 mm. Hg above the control levels, all drugs mentioned above except methoxamine induced ectopic pacemaker action, abnormal spontaneous beats, and abnormal and multiple responses to test stimuli (a stimulating electrode was attached to the right ventricle). All 4 drugs exhibited some degree of tachyphylaxis with respect to blood pressure maintenance. Methoxamine had a depressant action on the heart in that it prolonged the action potential and the absolute refractory period, raised the threshold to stimulation, and slowed atrioventricular conduction significantly (not due to reflex vagal action). All drugs tested decreased resting excitability.

RINZLER

Hendershot, L. C.: Cardiovascular Actions of a Bis-isothiourea. J. Pharmacol. & Exper. Therap. **123**: 1 (May), 1958.

The cardiovascular actions of 2, 2′- oxybis (p-phenylene-methylene) bisisothiourea were studied. In dogs intravenous doses of 0.1 mg. per Kg. produced an increase in blood pressure. Doses of 1.0 mg. per Kg. produced an initial, transient pressor response followed by a depressor response. Neither of these responses was blocked by vagotomy alone or in combination with carotid sinus denervation or by cervical spinal cord section. The pressor responses to norepinephrine and 1,1-dimethyl-4-phenylpiperazinium were enhanced after a single intravenous dose of the bisisothiourea. The drug also caused direct vasodilator effects in the perfused hind limb of the dog. It also produced reflex vasodilatation. Cutting the sciatic, femoral, and remaining cutaneous nerves abolished this reflex vasodilatation. Cardiac output was not reduced in the dog heart-lung preparation by large doses of bisisothiourea but responses to increased right atrial pressure were impaired. In the intact animal, the electrocardiogram was normal until just before death. There was no rise in plasma histamine levels in dogs and cats that received doses of bisisothiourea large enough to cause marked hypotension. Plasma histamine levels were increased following lethal or near lethal doses of bisisothiourea.

RINZLER

Baker, C. H., and Remington, J. W.: Acute Circulatory Collapse of the Adrenalectomized Dog Following Plasma Infusion. Circulation Research **6**: 294 (May), 1958.

Adrenalectomized dogs maintained on desoxycorticosterone acetate developed a fatal circulatory collapse when given normal dog plasma. Diphenhydramine prevented the collapse but its mechanism of action is not certain. Peripheral vasodilatation by histamine is not prevented

completely, so that one can only speculate if the antihistaminic or some other pharmacologic action is involved.

AVIADO

PHYSIOLOGY

Leusen, I., Demeester, G., and Bouckaert, J. J.: The effects of Muscle Work on the Circulation and Respiration of the Dog. Acta cardiol. **13**: 153, 1958.

In normal trained dogs, cardiovascular dynamics and ventilation were studied at rest and after exercise on a treadmill. In 16 animals data were collected on changes of the heart rate, blood pressure, and cardiac output (dye method) occurring 4 to 5 minutes after completion of exercise. In 6 dogs, ventilation and oxygen consumption were measured and in 6 others, the pH, oxygen and carbon dioxide concentrations and partial carbon dioxide pressures were determined in the arterial blood. Circulatory adaptations to exercise in normal dogs were comparable to reactions taking place in normal man. Regression curves derived from this study were presented and data of similar investigations by others, in which changes of the oxygen consumption were related to the changes of cardiac output and cardiac index, to the A-V difference and to the ventilation.

PICK

Darratt-Boyes, B. G., and Wood, E. H.: Cardiac Output and Related Measurements and Pressure Values in the Right Heart and Associated Vessels, Together with an Analysis of the Hemodynamic Response to the Inhalation of High Oxygen Mixtures in Healthy Subjects. J. Lab. & Clin. Med. **51**: 72 (Jan.), 1958.

Right heart catheterization was performed in 26 ambulatory healthy subjects using a no.-6 Cournand type catheter with birdseye tip, which was inserted by needle introduced percutaneously into a right anticubital vein and advanced into the right heart under fluoroscopic control. The zero reference point for all pressure measurements was mid-chest at the sternal end of the third interspace. The cardiac index averaged 3.5 and ranged from 2.5 to 4.4 liters per minute per square meter; the stroke index averaged 46 with a range from 37 to 63 ml. per beat per square meter of body surface area. The mean and range of values for calculated total systemic, total pulmonary, and pulmonary arteriolar vascular resistances were 1,130 (745 to 1,570), 205 (90 to 290), and 67 (44 to 106) dynes/sec./cm.$^{-5}$, respectively. The average pulmonary artery wedge was 15/9 mm. Hg, the average pulmonary artery pressure was 22/12 mm., the average right ventricular pressure was 27/4-10 mm., the average right atrial pressure was 9/4 mm. and the antecubital vein pressure was 9/7 mm. Hg; the radial artery pressure averaged 135/71 mm. of Hg. The average statistically significant mean pressure gradient from the antecubital vein, both venae cavae, and the left atrium to the right atrium were 2, 0.5, and 6 mm. Hg, respectively. The average systolic pressure gradient of 2 mm. Hg across the pulmonary valve was statistically significant. The effect of the administration of 95 per cent oxygen was investigated in 20 of these subjects. There was a fall in heart rate and an increase in stroke volume with no systematic change in cardiac output under these conditions. In addition, a fall in pressure throughout the right heart and pulmonary vascular tree and a rise in systemic arterial pressure were noted.

MAXWELL

PULMONARY DISEASES

Rose, J. C., and Lazaro, E. J.: Pulmonary Vascular Responses to Serotonin and Effects of Certain Serotonin Antagonists. Circulation Research **6**: 283 (May), 1958.

Serotonin is the most potent constrictor of the perfused lung vessels of the dog. Promethazine and lysergic acid diethylamide and its 2-brom derivative are the most potent antagonists to the constriction induced by serotonin. If serotonin is participating in the pulmonary hypertension of acute embolism, these antagonists deserve clinical trial.

AVIADO

Brachfeld, Jonas, Reale, A., and Goldberg, H.: Pitfalls in the Diagnosis of Pulmonary Hypertension. Am. Heart J. **55**: 905 (June), 1958.

The difficulties involved in defining a definite syndrome of primary pulmonary hypertension are pointed out. Before the diagnosis can be made the known causes of pulmonary hypertension must be ruled out. These include diseases of the pulmonary parenchyma, intracardiac or intervascular shunts, lesions of the pulmonary arterial vasculature other than those due to shunts, and obstruction of the pulmonary veins or of the mitral valve. Only with left heart catheterization can the diagnosis of primary pulmonary hypertension be established and surgically remediable lesions of the mitral valve be excluded. Three patients illustrating the problems involved are presented and discussed. In 1 patient who was tentatively diagnosed as suffering from primary pulmonary hypertension necropsy revealed the rare condition of endocardial fibrosis involving the mitral valve as the cause of the clinical picture. In another instance the patient was considered to have mitral stenosis until left heart catheterization demon-

strated the absence of a gradient across the valve and indicated the true diagnosis of primary pulmonary hypertension. The third patient presented had many features of interest in the study of pulmonary hypertension as well as a loud apical systolic murmur with mitral stenosis but without mitral regurgitation. Again, the correct diagnosis was made only after heart catheterization.

SAGALL

Mayer, E., Blazsik, C. F., and Rappaport, I.: Treatment of Pulmonary Insufficiency by Trachial Fenestration. J.A.M.A. **167:** 696 (June 7), 1958.

Tracheal fenestration provides a permanent access to the deeper airways. Four patients who were approaching terminal hypoxia as a result of destructive pulmonary disease were definitely benefited by the ready removal of secretions through a tracheal fenestration stoma. Such patients with diminished pulmonary reserve are sensitive to the least interference with the patency of the airways in their lungs. They need an early and permanent tracheal opening through which intubation and aspiration of the deeper airways can be quickly and easily done. Such intubation and aspiration is an effective method of relieving hypoventilation crises and appears to be the best method of preventing such crises in progressive pulmonary insufficiency. Tracheal fenestration has been done in too few cases and clinical observations are too recent for a final opinion but preliminary results are so striking that this preliminary report is justified.

KITCHELL

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Flood, F. B., and Boller, R. J.: Diffuse Glomerulonephritis as a Complication of Subacute Bacterial Endocarditis. J.A.M.A. **167:** 701 (June 7), 1958.

A patient with a long history of abdominal surgery and recurrent fevers finally exhibited hematuria, oliguria, nitrogen retention, and uremia. Prior to death a pericardial friction rub was noted and melena appeared. Autopsy disclosed subacute vegetative endocarditis on an old rheumatic valvulitis, petechiae of the cecum, and subacute diffuse glomerulonephritis. Diffuse glomerulonephritis is relatively infrequent as a complication of subacute bacterial endocarditis and the precise nature of the relationship between the 2 remains to be established.

KITCHELL

Birkenfeld, L. W., Leibman, J., O'Meara, M. P., and Edelman, I. S.: Total Exchangeable Sodium, Total Exchangeable Potassium, and Total Body Water in Edematous Patients with Cirrhosis of the Liver and Congestive Heart Failure. J. Clin. Invest. **37:** 687 (May), 1958.

By the application of isotope-dilution methods, it is now possible to make accurate estimates in vivo of fluid and electrolyte in man. In this study 57 patients were studied with the use of Na^{24}, K^{42}, and D_2O as tracers. It was found that expressed as per cent of body weight, total body water was increased in patients with edema. Total body water averaged 58.6 per cent in men with cirrhosis and edema, 62.9 per cent in cardiac failure and edema, and 54.6 per cent in nonedematous hospitalized "controls." An increase in total body sodium was found in edematous conditions. The increase was noted with a determined per unit body weight, per unit of dry body weight, per liter of body water, or per milliequivalent of total potassium. Selective or disproportionate accumulation of sodium with heart disease beyond that associated with edema formation was not demonstrated. In all groups of patients, total exchangeable potassium was decreased below normal standards when referred to either body weight or dry body weight. Distinct differences in body composition, therefore, were found between edematous and edema-free patients. The authors, however, point out the limitations in the interpretation of these data.

WAIFE

RHEUMATIC FEVER

Massie, R. W. and Stahlman, M.: Serum Oxaloacetic Transaminase Activity in Acute Rheumatic Fever. J. Dis. Child. **95:** 469 (May), 1958.

This is a report of 18 patients, 16 children and 2 adults, seen at the Vanderbilt University Hospital with active rheumatic carditis in whom serum transaminase levels were followed over a period of time and correlated with other laboratory tests indicative of rheumatic activity. The transaminase levels were sometimes elevated in patients with acute rheumatic fever and active rheumatic carditis, but there was no correlation between the presence of carditis and the elevation of transaminase levels. Single determinations were found to be useless. The only value was in following repeated determinations over a long period of time. Salicylate therapy affected the transaminase levels, but not consistently, for it both raised and lowered the transaminase levels in several patients after administration. The rise in transaminase levels was correlated quite well with the rise in sedimentation rate, C-reactive protein and antistreptolysin O titers, but in no definite correlative relationship.

HARVEY

Waaler, E.: Rheumatic Fever and Rheumatic Heart Disease. I. Incidence and Sex Distribution. Acta med. scandinav. **160:** 281, (March 29), 1958.

In order to study the incidence of acute and chronic rheumatic valvular disease as a cause of death as well as their distribution in the 2 sexes, the author made a study of the autopsy material derived from the Gade Institute, Bergen, Norway, for the period 1941-1955. In all there were 5,470 autopsies, of which 219 were classified as rheumatic heart disease, chronic or acute. Rheumatic heart disease ranked second along with hypertensive heart disease as the cause of death among the heart diseases. Arteriosclerotic heart disease occupied the number one position. The 15-year period studied did not reveal any fall in the total incidence of rheumatic heart disease in the autopsies. The fall in morbidity from the disease had not been reflected in the autopsy material. Acute pancarditis did not occur in the last half of the period under study. The difference in incidence in the 2 sexes, 82 males and 137 females, was statistically significant There was also evidence suggesting that females were not only more often affected but that they also had a relatively greater number of severe cases. The greater incidence of rheumatic heart disease in females was due to its more frequent occurrence in females above 40 years of age. Below 40 years there were an equal number of cases of either sex. Rheumatic heart disease occurred as commonly in the autopsies in Oslo as in Bergen. The supposition that rheumatic fever in earlier years was more common in Bergen than in Oslo was not substantiated.

BROTHERS

Wilson, M. G., Lim, W. N., and Birch, A. M.: The Decline of Rheumatic Fever. Recurrence Rates of Rheumatic Fever among 782 Children for Twenty-one Consecutive Calendar Years (1936-1956). J. Chron. Dis. **7:** 183 (March), 1958.

In this article consecutive records of 782 children born after 1916 who were under continuous, uniform, medical supervision during a 40-year period at the New York Hospital Cardiac Rheumatic Clinic, were reviewed. Recurrence rates of the major manifestations of rheumatic fever for ages 2 through 20 years were calculated for the period 1936 through 1956. There was a statistically significant downward trend, with a slope of 0.4 per cent per year, in the annual recurrence rates from 1937 to 1956. The mean annual recurrence rate for those with a recent attack (within 2 years) was 21.4 per 100 person years, 3 times the rate of 6 per cent for children free from a rheumatic attack for 2 or more years. There was a significant decline in the recurrence rate in both groups over the years. A comparison of aged specific recurrent rates over the periods 1916 to 1943, and 1944 to 1956, revealed lower rates at almost every age in the latter period. The approximate chance of a recurrence in any 1 year for all children 6 to 13 years of age declined from 1 to 4 before 1944, to 1 in 7 between 1944 and 1956; and for ages 14 to 20 the chances fell from 1 in 16 to 1 in 35. The general improvement in the standard of living in greater New York City over the past 2 decades was reflected in the socioeconomic composition of the Clinic population. The relative percentage of patients in the best environmental group increased, and those in the poorest socioeconomic status decreased. Recurrence rates were generally lower in the more favorable environmental groups; and recurrence rates for the poorest environmental groups did not reveal the decline noted for the total Clinic population. The initial decline in recurrence rates antedated the antimicrobial era.

MAXWELL

ROENTGENOLOGY

Logan, W. D., and Goudelock, W. J.: Arteriographic Errors in Localization of Acute Arterial Obstruction. Surgery **43:** 974 (June), 1958.

A 56-year-old man was admitted to the hospital with findings suggestive of a popliteal embolus. Arteriography, however, indicated the point of obstruction to be in the superficial femoral artery. This area was surgically explored but no embolus was found. The area of the popliteal artery was then explored and an embolus was located and removed. This erroneous localization of arterial obstruction by the arteriogram led the authors to conduct a series of experiments in dogs. Arterial obstruction was produced in the animals by introducing emboli in the form of lead pellets. Arteriograms were then obtained. In all animals in which the obstruction was complete, a segment of artery proximal to the obstruction was not visualized with the arteriograms. Subsequent autopsy failed to reveal any thrombosis to account for this lack of filling. The lack of filling was apparently due to a static column of blood proximal to the point of obstruction. The arterial spasm occurring after traumatic arterial injury might also produce a similar picture. When emboli obstruct an artery in 1 branch of a bifurcation there is no static column of blood and localization of the obstruction is more accurate. It is concluded that in acute arterial obstruction from either emboli or trauma, the presence of a proximal static column of blood must be considered in interpretation of the arteriograms.

BROTHERS

Bellman, S., and Frank, H. A.: Experimental Coronary Arteriography. J. Thoracic Surg. **36**: 33 (July), 1958.

A method for direct coronary angiography in the surgically exposed dog heart is described. A coronary artery branch was cannulated with a heparin-filled polyethylene tube through which 10-ml. injections of Hypaque can be made for radiography. The procedure was found to be well tolerated even when multiple injections were made at 5-minute intervals. Electrocardiograms showed bradycardia and transient T-wave changes, even when physiologic saline was used instead of the contrast material. The chief hazard was the risk of ventricular fibrillation, which appeared to be associated with anoxia and anesthesia problems. The quality of the radiograms obtained was unusually high. Single exposure arteriograms revealed coronary vessels down almost to limit of naked-eye resolution. The method seems suitable for its intended purpose of delineating coronary arteries in association with experimental surgical procedures.

ENSELBERG

Grishman, A., Khilnani, M. T., and Jick, S.: The Pulmonary Radiographic Changes of Mitral Disease; Mitral Lung Disease. J. Mount Sinai Hospital, **25**: 291 (July-August), 1958.

Radiographic findings in 105 patients with mitral disease were reviewed. All the patients had clinically significant symptoms. Four varieties of pulmonary roentgenographic patterns were encountered: diffuse granular pattern, Kerley lines (interlobular septal lines), nodular ossification and hemosiderosis. Among patients with mitral stenosis, with or without mitral insufficiency, the diffuse granular pattern was found in 60 per cent; Kerley lines in 35 per cent; and nodular ossification and hemosiderosis in about 15 per cent each. The diffuse granular pattern was associated with normal as well as elevated resting pulmonary artery pressures, as was also the pattern of nodular ossification. Septal lines and pulmonary hemosiderosis were found only with elevated pulmonary artery and capillary pressures. None of the above pulmonary abnormalities were seen in patients with pure mitral insufficiency, though septal lines were unexpectedly found in 3 patients with aortic valve disease. Interlobular septal lines were also found in lymphangitic carcinomatosis, sarcoid, silicosis, and anthracosis. Nodular ossifications have not been found in any other heart disease but mitral stenosis.

ENSELBERG

Steiner, R. E.: Pulmonary Hypertension. A Symposium, II. Radiological Appearances of the Pulmonary Vessels in Pulmonary Hypertension. Brit. J. Radiol. **31**: 188 (April), 1958.

The radiologic appearances of the pulmonary arteries and veins are influenced by the pulmonary vascular pressures and blood flows. A radiologic study may be all that is needed for precise diagnosis thus eliminating cardiac catheterization in many instances. Two definite groups of radiologic patterns are seen. The first is a marked pulmonary plethora with dilated arteries due to increased flow in congenital heart disease cases, such as septal defect (atrial or ventricular), and patent ductus arteriosus. The second is due to increased resistance with 2 subgroups where there are increases in either postcapillary or precapillary resistances. In postcapillary resistance there is elevation in pulmonary venous pressure with engorged veins, some pulmonary arterial distention, and a background pattern of interstitial pulmonary edema. Such patterns are seen in mitral stenosis, left atrial tumor or thrombus, and left ventricular failure. In increased precapillary resistance one sees pulmonary arterial hypertension with marked main pulmonary artery distention and relative narrowing of peripheral pulmonary arteries. This may be found in mitral stenosis (here secondary to postcapillary resistance), congenital heart disease, pulmonary heart disease, repeated pulmonary emboli, primary pulmonary hypertension, and in pulmonary arteritis.

KITCHELL

SURGERY AND CARDIOVASCULAR DISEASE

Nachlas, M. M., Myers, M. J., Solomon, R. D., Kelly, A. B., and Seligman, A. M.: Maintenance of Patency of Carotid Arteries Implanted Into the Myocardium. J. Thoracic Surg. **35**: 699 (June), 1958.

The present study was an extension of the authors' investigations into the Vineberg procedure of implanting the left mammary artery into a myocardial tunnel. In all but 2 of 44 experiments the lumen of the implanted artery became obliterated within 4 weeks. The authors then decided to use an artery of larger caliber in which 1 tangential opening 4 mm. in diameter was made. When the left carotid artery was used in place of the mammary artery, they found excessive narrowing of the lumen in 13 of 14 cases. This was usually caused by intimal proliferation. Previous work had implied that maintenance of blood flow through the implanted vessel might prevent narrowing or closure. The authors therefore modified their procedure so that the distal open end

of the carotid artery was placed in the cavity of the right ventricle. This resulted in patency of the implanted vessels in all cases, in some for as long as a 10-month observation period.

ENSELBERG

Lewis, F. J.: High Defects of the Atrial Septum. J. Thoracic Surg. **36**: 1 (July), 1958.

The most frequent type of atrial septal defect is the foramen ovale type (78 per cent of the author's series of 66 patients; the least frequent is the low defect, or persistent ostium primum. The high defect has been the second most common type in the author's experience (12 out of 66 patients). The author describes the anatomy of the high defect and the surgical problems associated with it. The high defect has no definite margin superiorly, and has therefore been called an abnormal entry of the superior vena cava into both atria. In addition there is invariably associated partial anomalous pulmonary venous drainage, veins draining the right upper and middle lobes entering the superior vena cava just above the defect. To repair this defect the author has used a row of sutures placed so that the aberrant pulmonary veins are directed into the left atrium as the defect is closed. There have been several complications, the most serious of which was venous thrombosis at the site of repair. Several improvements in technic are offered. One of them consists of closing the defect but leaving the highest abnormal pulmonary vein intact. Another method is to revise the vena caval opening so that it drains entirely into the left atrium, along with the aberrant pulmonary veins. Then the superior vena cava is divided above the pulmonary veins and anastomosed to the right atrium.

ENSELBERG

Denman, F. R., Brown, W. G., Skinner, S. J., Fitch, E. A., and Glass, H. G.: Fate of Human Aortic Homografts Ten, Twenty-Four, and Twenty-Seven Months After Transplantation. Arch. Surg. **76**: 944 (June), 1958.

Both a 24-month and a 10-month homograft were obtained at autopsy from the same patient, a 64-year-old man with arteriosclerotic heart disease and an aneurysm of the abdominal aorta below the renal arteries. The grafts were utilized at different times to replace the aneurysm. The homograft removed after transplantation for 24 months had been preserved in Gross' medium, while the 1 transplanted for a 10-month period was lyophilized. Upon examination, definite aneurysmal dilatation was apparent in the 24-month graft. Microscopically, there was evidence of degeneration, fragmentation, and loss of elastic fibers at the site of the aneurysm, and arteriosclerotic changes were present throughout the graft. When the 10-month graft was originally inserted, a broad sling of a polyvinyl material was placed around it to hold it in place. At this junction the homograft showed an aneurysmal dilatation believed to be the result of pressure necrosis from pulsatile trauma. Microscopically there was little structural degeneration and good union to the host aorta. The 27-month homograft was lyophilized and had been used to replace an aneurysm of the abdominal aorta below the renal arteries and involving the bifurcation. Postmortem examination revealed moderately advanced atheromatous changes in the graft similar to those in the host aorta. Despite these observations of degeneration and arteriosclerotic changes in homografts, the authors believe that they maintain their functional integrity for long enough time to recommend their continued use until a better substitute is found.

BROTHERS

Theodotou, C. B.: Intravascular Pressure Changes in the Carotid System Following Ligation of the Common and External Carotid Arteries. Surgery **43**: 824 (May), 1958.

Direct recording of arterial and pulse pressures was obtained during various occlusions of the carotid system in 8 patients who had occlusion of the common carotid artery for aneurysms or fistulas. These observations presented 2 facts useful in the clinical management of patients needing carotid ligation. First, the gradual occlusion of the carotid artery by the Selverstone clamp as usually practiced produces no appreciable reduction of pressure with the first turns. All the reduction will appear at a specific point in closure of the clamp. Effective closure can be hastened by obtaining measurements of the pressure on the operating table, thereby eliminating the first ineffective turns. The critical turn can then be carried out in very small daily increments of one-quarter turn or less. Secondly, and thought to be of more importance, was the observation that in addition to reduction of arterial pressure, complete damping of the pulse pressure is also obtained. Damping of the pulse pressure could be considered a disadvantage because it has been shown experimentally that a continuous pressure is more likely to cause saccular formation in the form of varicosities. However, the reduction in mean arterial pressure neutralizes this possibility. The author also recommends ligation of the external carotid below the origin of the superior thyroid artery because of the considerable amount of collateral circulation possible via the superior thyroid artery. Use of the

Selverstone clamp or other flat type of occlusive material instead of a round ligature seems to diminish the likelihood of aneurysmal formation at the site of ligation.

BROTHERS

UNCOMMON FORMS OF HEART DISEASE

Eisenstein, B., and Taubenhaus, M.: Nonsyphilitic Interstitial Keratitis and Bilateral Deafness (Cogan's Syndrome) Associated with Cardiovascular Disease. New England J. Med. **258:** 1074 (May 29,) 1958.

Three patients with nonsyphilitic interstitial keratitis and vestibuloauditory symptoms of the type known as Cogan's syndrome are presented. In 2 of these systemic cardiovascular disease of undetermined etiology was found. One patient developed aortic insufficiency due to a valvulitis which led to valvular aneurysm formation, perforation of an aortic cusp, congestive heart failure, and death. Autopsy revealed a healed endocarditis, with unusual fibrinoid degeneration of the aortic valves, as well as arteritic changes in the small branches of the coronary arteries resulting in multiple small myocardial infarctions. The second patient developed an extensive necrotizing angiitis. In the third patient there were no systemic manifestations. A review of the literature also indicated a relatively high prevalence of cardiovascular disease in these patients and this suggests that Cogan's syndrome may represent a part of a more generalized disease in which the heart and small vessels may be involved.

SAGALL

VALVULAR HEART DISEASE

Wegria, R., Muelheims, G., Golub, J. R., Jreissaty, R., and Nakano, J.: Effect of Aortic Insufficiency on Arterial Blood Pressure, Coronary Blood Flow and Cardiac Oxygen Consumption. J. Clin. Invest. **37:** 471 (March), 1958.

The occurrence of chest pain in patients with aortic insufficiency and without disease of the coronary arteries has often been ascribed to a decrease in coronary blood flow. Presumably, aortic insufficiency decreases the coronary blood flow by lowering the mean aortic diastolic pressure. This paper reports a study on dogs to elucidate the phenomenon. Aortic insufficiency was produced surgically and hemodynamic studies were performed in 8 animals. Aortic insufficiency lowered the mean arterial blood pressure. Nevertheless, despite the sudden drop in mean arterial pressure, the coronary blood flow rose in all experiments in amounts ranging from 12 to 36 per cent. There was also an increase in oxygen consumption due to the coronary blood flow alone, for the coronary blood oxygen arteriovenous difference was unchanged. These data indicate that acute aortic insufficiency increases cardiac oxygen consumption and coronary blood flow even when aortic insufficiency is severe enough to produce a fall in aortic diastolic pressure. These results are in disagreement with other published experiments on anesthetized dogs, and the authors discuss the possible reasons for these differences. It was concluded that the increased coronary flow must be due to a decrease in resistance of the coronary bed, which, in turn, may have been induced by the increase in the work of the left ventricle.

WAIFE

VASCULAR DISEASE

Pauporte, J., Lowenstein, J. M., and Davison, R.: Blood Turnover Rates Distal to an Arteriovenous Fistula. Surgery **43:** 828 (May), 1958.

Using a radioactive dye (I^{131} rose bengal) and an external gamma-ray detection system, measurements were made of the blood turnover rates in the thigh and tibia of dogs with artificially created femoral arteriovenous anastomoses (AVA) of varying sizes. Blood turnover rate is the same as the clearance rate—the number of times each minute that the local blood pool is replaced by fresh blood. In control (unoperated) limbs turnover rates in tibia and thigh were very nearly the same. Muscle (thigh) values were unreliable in limbs with AVA because tracer material injected into the femoral artery near the large shunt was subject to turbulence and reverse flow. Tibial dilution curves were satisfactory. Immediately following creation of the AVA, flow distal to the AVA was in all cases less than in the control side. The larger the AVA, the less the tibial blood flow. Flow distal to the AVA generally increased with time, approaching normal values 8 weeks after operation. The return of tibial blood flow to normal values is believed to be due to the development of collateral circulation.

BROTHERS

Shaw, R. S., and Maynard, E. P., III.: Acute and Chronic Thrombosis of the Mesenteric Arteries Associated with Malabsorption: A Report of Two Cases Successfully Treated by Thromboendarterectomy. New England J. Med. **258:** 974, (May), 1958.

Two patients with atherosclerotic occlusive disease of the superior mesenteric artery are reported. In 1, acute mesenteric artery thrombosis was associated with transient postoperative mal-

absorption. In the other chronic mesenteric artery thrombosis led to a clinical picture of intestinal malabsorption, intermittent abdominal pain, weight loss, and eventual acute intestinal infarction. In both patients surgical relief was obtained by thromboendarterectomy. These 2 patients illustrate that intestinal ischemia may be associated with malabsorption and that both the acute and the chronic forms of thrombosis of the mesenteric arteries are amenable to reconstructive surgery.

SAGALL

Gibbs, N. M.: Venous Thrombosis of the Lower Limbs with Particular Reference to Bed-Rest Brit. J. Surg. 45: 209 (Nov.), 1957.

This article offers an extensive review on the subject, as well as the author's experience with 253 patients who died in hospitals and who subsequently had the veins of the lower leg and thigh dissected. Because of the anatomy of the intermuscular veins of the lower limbs, the author thinks that they are particularly susceptible to thrombus formation with slowing or other abnormality of blood flow. He offers evidence for concluding that alteration in coagulability of blood and primary endothelial lesions probably do not play a large part in the development of thrombosis. There is a detailed anatomic description of the veins of the lower leg and thigh with excellent necropsy venograms. In particular, the author points out that veins of the soleus muscle are susceptible to venous stasis. Thrombus was found in veins of the lower limb in 59 per cent of the 253 patients. The highest incidence of thrombus formation was found in the intramuscular veins of soleus and also in the peroneal and posterior tibial veins. Thrombus was found on dissection of the thigh veins in 63 patients. A total of 91 lower limbs was involved, and of these the thrombus was continuous with thrombosis of the leg veins in 59 limbs. Thrombosis of the thigh was bilateral in 31 cases and unilateral in 29 cases. In 38 lower limbs the thrombus was isolated to the thigh veins and had arisen from them. In the over-all series it was found that thrombosis of the thigh vein occurred in approximately 10 per cent of cases of calf vein thrombosis. Ileofemoral and ileocaval thromboses were found in a total of 15 cases and in the majority represented an extension of the thrombus from the lower limb. There were only 2 cases of isolated thrombosis in the iliac vein or the inferior vena cava. The first case was associated with a strangulated femoral hernia, and the second case with a pelvic inflammatory mass. The incidence of thrombus formation showed a direct correlation with duration of confinement in bed. The incidence of organized thrombi found post mortem steadily increased with duration of bedrest while the incidence of nonorganized thrombi steadily decreased to the fourth to fifth week. The incidence of pulmonary embolism in association with leg vein thrombosis rose to a maximum in 2 to 3 weeks of bed confinement with slow decline in subsequent groups up to 12 weeks. The peak incidence of pulmonary embolism did not correspond to the peak incidence of nonorganizzed thrombi which was found in those patients dying in their first week of bed confinement. The most important factor in the etiology of venous thrombosis of the leg is cited as immobilization, and the importance of early ambulation as a prophylactic measure is stressed. Anticoagulants are mentioned as being of use in preventing local extension of the thrombus and possibly preventing further damage to the veins of the lower limb.

MAXWELL

Millikan, C. H., Siekert, R. G., and Whisnant, J. P.: Anticoagulant Therapy in Cerebral Vascular Disease—Current Status. J.A.M.A. 166: 587 (Feb. 8), 1958.

In the therapy of strokes, attention should be directed to several facets: prevention of the first attack, prevention of extension after an attack, and prevention of multiple attacks. In solving these problems, anticoagulants (heparin, ethyl biscoumacetate, and bishydroxycoumarin) were used in 317 patients with manifestations of cerebral vascular disease. Indications for the selection of patients for therapy were intermittent insufficiency in the vertebral-basilar system, intermittent insufficiency in the carotid system, thrombosis in the vertebral-basilar system with infarction, and actively advancing occlusion of the carotid system. A fifth indication suggested by others than the authors is multiple thromboembolic episodes. In the total of 317 patients, 179 were treated for the syndromes of intermittent insufficiency and 172 of these experienced cessation of the attacks. Only 9 deaths occurred in 107 treated patients with thrombosis in the vertebral-basilar system and infarction. Of 31 treated patients with actively advancing occlusion of the carotid system, 29 had no progression of neurologic deficits. A definite clinical impression exists that anticoagulant therapy is of benefit in these cases. However, evidence is tenuous that anticoagulants can cause dissolution of a thrombus once established and there is no evidence that anticoagulants have any beneficial action on infarcted brain.

KITCHELL

McGarity, W. C., and Logan, W. D., Jr.: Multiple Peripheral Arterial Emboli. Surgery **43**: 254 (Feb.), 1958.

Sixty-four patients with a total of 86 peripheral, arterial emboli were encountered in a 6 year period (1950-1956) at the Grady Memorial and Veterans Administration Hospitals in Atlanta, Georgia. Sixteen patients had multiple emboli and accounted for 38 of the total number. Atrial fibrillation and myocardial infarction were the chief causes of multiple emboli. In no instance was subacute bacterial endocarditis encountered. Treatment for multiple emboli is essentially the same as for any single embolus. Embolectomy is the treatment of choice when the patient's condition permits and collateral circulation to the part involved is deemed adequate. In the presence of adequate collateral circulation sympathetic blocks, anticoagulants, and the oscillating bed give good results. In this series, regardless of the type of treatment used, results were better in patients with multiple emboli than in those with single emboli. There were 3 deaths in the group with multiple peripheral emboli and 16 deaths in the patients with single emboli. A second embolic episode occurred within a relatively short time, usually within a year, in one third of the patients surviving the first embolus. Prophylactic anticoagulant therapy seemed to be of definite value in preventing the recurrence of an embolic event.

BROTHERS

McGarity, W. C., Logan, W. D., Jr., and Cooper, F. W., Jr.: Peripheral Arterial Emboli. Surg. Gynec. & Obst. **106**: 399 (April), 1958.

The clinical course of 64 patients having a total of 86 arterial emboli is described. Eighty-six per cent of emboli were thought to arise from rheumatic or arteriosclerotic hearts, so that the great majority of patients were over 40 years old. The commonest embolic sites were at the bifurcation of the femoral arteries(42 per cent), the popliteal arteries (17 per cent), the brachial arteries (16 per cent), and the iliac arteries (15 per cent). The treatments of choice are summarized including surgical approaches, anticoagulants, and sympathetic blockade. The circulation was restored in 36 of 50 instances after embolectomy and in 17 of 36 instances of treatment by other means. The mortality of 12 patients in the former and of 7 in the latter group largely resulted from associated diseases. While the management of a patient having an embolus must be individualized, those lodging in the aorta, iliac, or femoral arteries generally constitute an emergency for surgical removal.

ROGERS

Mowlem, R.: Lymphatic Oedema—An Evaluation of Surgery in Its Treatment. Am. J. Surg. **95**: 216 (Feb.), 1958.

The mechanics of edema formation are reviewed. In 2 common conditions in which edema occurs, it is obvious that there is failure of lymphatic function. One is an obstructive lesion, usually found in the arm following radical axillary adenectomy or radiation for carcinoma. The other is the so-called idiopathic lymphedema, apparently due to hypoplasia of the lymphatic tree, usually seen in the legs and characterized by swelling that begins in the ankle region and extends, proximally. Despite certain similarities in their clinical picture and life history, the causal mechanism is different in the 2 conditions, leading to different methods of treatment. The surgical methods available are reviewed and the indications for their use are considered. A recent technic applicable to the arm in obstructive edema makes use of a wick of tissue derived from the opposite side of the body, which is presumed to be normal and is so arranged as to bypass the obstruction in the axilla. Lymph reaching the lower end of the pedicle crosses the midline of the body to be discharged into the opposite axilla. This treatment will prevent the edema from becoming worse but will have no effect upon the fibrosis already produced. An additional simple wedge reduction of a bulky, fibrotic limb may sometimes be beneficial. In idiopathic lymphedema the efficacy of the lymphatic system is negligible. Treatment must depend upon a recognition of this fact and is directed toward an increase in the patients' comfort and mobility by reducing the thickness and bulk of the subcutaneous tissue in the effected area. Present methods of handling lymphedema are inadequate to produce normality because of lack of knowledge of the basic pathology of the problem.

BROTHERS

OTHER SUBJECTS

Kaplan, M. H.: Localization of Streptococcal Antigens in Tissues. I. Histologic Distribution and Persistence of M. Protein, Types 1, 5, 12, and 19 in the Tissues of the Mouse. J. Exper. Med. **107**: 341 (March), 1958.

A method is described for the detection of streptococcal antigens in tissues employing an indirect immunofluorescent technic. By use of this method in the mouse it was found that the histologic localization and the rates of disappearance of M proteins of types, 1, 5, 12, and 19 were similar and comparable. The major sites of deposition were the endocardium and adjacent subendocardium of the heart, alveolar walls of the lung, glomerular tufts of the kidney, and reticulo-

endothelial cells of the liver, spleen, lymph nodes, and adrenal gland. Lesser concentrations were found in capillary endothelium and connective tissue sites in myocardium, kidney, skin, and gastrointestinal tract. After injection of 0.5 mg. of M-protein fraction, the concentration of antigen diminished to undetectable levels in all organ sites by 4 days except in the renal glomerulus, where traces were visible at 8 days. In mice injected with streptococcal culture intraperitoneally, M protein was found at sites of focal abscesses in the liver and spleen, and on the serous surfaces of these organs. The histologic distribution of M protein was compared with that described previously for pneumococcal polysaccharide and animal protein and the differences in the extent of distribution and in the characteristics of antigen deposition are pointed out.

SAGALL

Paplanus, S. H., Zbar, M. J., and Hays, J. W.: Cardiac Hypertrophy as a Manifestation of Chronic Anemia. Am. J. Path. **34**: 149 (Jan.-Feb.), 1958.

A study on 10 dogs was undertaken to determine the effect of uncomplicated anemia upon cardiac size. Anemia was produced in 5 dogs by weekly bleedings. Adequate nutrition was maintained and no depletion of protein in the experimental dogs took place. After 5 months of this regimen the control and experimental animals were sacrificed; the hearts were weighed and subjected to the scrutiny of an experienced pathologist for consideration of hypertrophy. The weight of the hearts in the experimental animals was statistically significantly increased over the control animals. The opinion of the experienced pathologist regarding hypertrophy in the experimental animals was statistically significant in the prediction of hypertrophy from simple examination. Water content of the heart muscle was measured and did not vary in the experimental and control animals, thus edema could not be the factor causing increase in the heart's weight. This study showed that hypertrophy of the heart does occur from chronic anemia, and this hypertrophy involves both right and left ventricles and is accompanied by dilatation of all chambers of the heart.

HARVEY

Cobbs, B. W., Shillingford, J. P., and Steiner, R. E.: The Size of the Left Atrium in Conditions Other Than Mitral Valve Disease. Brit. Heart J. **19**: 495 (Oct.), 1957.

The volume of the left atrium was measured within 6 to 72 hours after death by filling a condom within the left atrium to a pressure of 30 cm. of water after the mitral valve had been closed by an inflated condom inserted in the left ventricle. Fifty-three normal hearts and 110 with a variety of diseases were studied. The normal left atrial volume was related to body height. In the male, it varied from 60 to 115 ml. and in the female from 60 to 90 ml. The largest left atria occurred in mitral valve disease, but enlargement occurred in those with hypertension, coronary arterial disease and aortic valve disease, particularly if failure had been present. Left atrial enlargement could usually be detected radiologically if the volume was over 120 ml. by the lateral projection as well as by the oblique views.

SOLOFF

Gilchrist, A. R.: Clinical Aspects of High-Grade Heart-Block. Scottish M.J. **3**: 53 (Feb.), 1958.

The author reviews his experiences with 140 patients with high-grade heart-block on whom adequate data and follow-up records were available. It is emphasized that the development of chronic complete block in man generally does not follow the usual physiologic concepts derived from animal experiments. The term "high-grade" block is used by the author to include in addition to complete block, a type of incomplete block characterized by dropped beats (usually 2:1 or 3:1 rarely 4:1) not associated with Wenckebach periods. This type can be further distinguished from the more benign type of incomplete block by its response to exercise or atropine. When either of the latter agents is sufficient to accelerate the atrial rate significantly, the Type I cases will respond by a temporary reduction or disappearance of block, whereas the Type II cases will develop higher grades of block. Occasionally, also, the Type II cases may respond to vagal stimulation by a paradoxical increase in ventricular rate consequent to a decline in atrial rate. The differentiation is important because the Type II cases are apt to exhibit Adams-Stokes attacks or develop complete block. Many other observations on heart-block were also made. Complete block in the course of acute infarction may be overlooked because the ventricular rate is usually faster than in chronic cases, the average being 54. Persistent complete block may develop suddenly in the course of congenital heart disease and calcific aortic stenosis. The gradual development of complete block may occur in the course of a few weeks or as long as 9 years in patients with a history of recurrent fainting fits but no other significant findings. Not all cases of chronic complete block are permanent. Even after as long as 22 years normal rhythm may be resumed.

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NEW OFFICERS OF ASSOCIATION ELECTED AT ANNUAL MEETING

A. Carlton Ernstene, M.D., Chairman, Division of Medicine, Cleveland Clinic, was chosen as President-elect of the American Heart Association by the national Assembly at the Annual Meeting in San Francisco last October. At the same meeting, Francis L. Chamberlain, M.D., Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, was installed as President for the 1958-1959 term.

Retiring President Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine, became Chairman of the Heart Association's Central Committee for Medical and Community Program.

Newly elected as Vice Presidents of the Association were A. Wilbur Duryee, M.D., New York, and Ray B. Wiser of San Francisco. Continuing as Vice Presidents are: George E. Burch, M.D., New Orleans; Irving B. Hexter, Cleveland; Kenneth G. Kohlstaedt, M.D., Indianapolis; Frank L. Mechem, Seattle; Oglesby Paul, M.D., Chicago; Louis E. Viko, M.D., Salt Lake City; and Sylvester L. Weaver, Jr., New York.

NOVEMBER-DECEMBER ISSUE OF AHA-SPONSORED HEART BULLETIN CONTAINS NOTABLE MATERIAL

The attention of *Circulation* readers is drawn to the November-December issue of "The Heart Bulletin" which reflects the new editorial policy of the publication under sponsorship of the American Heart Association, in cooperation with the National Heart Institute and the American Academy of General Practice.

Six notable contributions which combine high scientific standards with the faculty of interpreting difficult medical problems to the practicing physician are published in the November-December issue of the Bulletin as follows:

"The Postmyocardial Infarction Syndrome," William Dressler, M.D.; "Chlorothiazide in Hypertension," Edward D. Freis, M.D.; "Rehabilitation of the Cardiac Patient: Energy Cost in Prescription of Work Dosage," Edward E. Gordon, M.D.; "Pulmonic Stenosis with Intact Ventricular Septum," Dwight C. McGoon, M.D.; "Electrocardiographic Aspects of Hypopotassemia," Eugene Lepeschkin, M.D. and Borys Surawicz, M.D.; and "Renal Hypertension," Harriet P. Dustan, M.D. and Eugene Poutasse, M.D.

Heart Associations are promoting "The Heart Bulletin" as one of the outstanding publications of professional information for the practicing physician. In many areas, the publication is being made available to physicians by courtesy of their local Heart Associations.

The Medical Arts Publishing Foundation, Houston, which initiated "The Heart Bulletin" in 1952 as a public service, continues to publish the journal.

RHEUMATIC FEVER CONFERENCE MATERIALS ARE AVAILABLE

Interested physicians may obtain from their local Heart Associations a summary of the sessions and the recommendations of the Conference on Rheumatic Fever Secondary Prevention Programs held in Chicago, March 9-10, under sponsorship of the Heart Association and the U.S. Public Health Service. Also available is an anthology of ten rheumatic fever secondary prevention programs which were compiled as study material for the Conference.

3,600 PHYSICIANS ATTEND WORLD CARDIOLOGY CONGRESS

More than 3,600 physicians and scientists from all parts of the world participated in the Third World Congress of Cardiology in Brussels, September 14 to 21. Over 500 papers on all aspects of cardiovascular disease were presented and discussed at various round tables and symposia.

SCIENCE ASSOCIATION SPONSORS SYMPOSIUM ON CONGENITAL HEART DISEASE

The American Association for the Advancement of Science, Section on Medical Sciences, has scheduled a symposium on Congenital Heart Disease at its Annual Meeting at the Sheraton Park Hotel, Washington, D.C., December 29-30, 1958.

The symposia are supported by a grant from the National Heart Institute and endorsed by the American Heart Association and the American College of Cardiology. Two of the four sessions of particular interest to physicians will be held on December 30. They include "The Diagnosis of Congenital Heart Disease," with André Cournand, New York, presiding, and "Surgical Therapy of Congenital Heart Disease," Alfred Blalock, Baltimore, presiding.

Subjects to be covered during the morning session on December 30 include "Cardiac Catheterization Techniques Using Pressure, Flow, and Oxygen Analysis," Lewis Dexter, Boston; "Indicator—Dilution Technics," Earl H. Wood, Rochester, Minn.; "The Characterization of Circulatory Shunts with Foreign Gas Technics," Eugene Braunwald, Bethesda, Md.; "Cinecardioangiography in the Diagnosis of Congenital Lesions," F. Mason Sones, Jr., Cleveland; "Intracardiac Phonocardiography in the Diagnosis of Congenital Heart Disease," David Lewis, Philadelphia; and "Relative Role of Various Clinical and Hemodynamic Techniques in Diagnosis of Congenital Heart Disease and in Selection for Surgery," Howard B. Burchell, Rochester, Minn.

The afternoon session on "Surgical Therapy of Congenital Heart Disease" includes "The Surgical Treatment of Pulmonary Valvular Stenosis and Atrial Septal Defect Using Hypothermia," Henry Swan, Denver; "Ventricular Septal Defects and Aneurysms of the Sinus of Valsalva," C. Walton Lillehei, Minneapolis; "The Surgical Treatment of Cyanotic Congenital Heart Disease," John W. Kirklin, Rochester, Minn.; "Problems of Extracorporeal Circulation," Robert Gross, Boston; and "Present Status and Future Trends in the Surgical Therapy of Congenital Heart Disease," Denton Cooley, Houston, Tex.

Information regarding the symposia may be obtained from Raymond L. Taylor, M.D., American Association for the Advancement of Science, 1515 Massachusetts Avenue, N.W., Washington 5, D.C.

MEETINGS CALENDAR

December 12-13: American Federation for Clinical Research, Eastern Section, Boston. William B. Schwartz, New England Center Hospital, 171 Harrison Avenue, Boston 11, Mass.

January 22-24: American Federation for Clinical Research, Southern Section, New Orleans. Ellard M. Yow, Baylor University College of Medicine, Houston 25, Tex.

January 28-29: American Federation for Clinical Research, Western Section, Carmel, Calif. Richard J. Havel, University of California Medical Center, San Francisco 22, Calif.

March 17-19: National Health Council, Chicago. Philip E. Ryan, 1790 Broadway, New York 19, N.Y.

April 6-9: American Academy of General Practice, San Francisco. Mac F. Cahal, Volker B'lvd. at Brookside, Kansas City 12, Mo.

April 15-17: American Surgical Association, San Francisco. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 20-24: American College of Physicians, Chicago. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

ABROAD

February 19-21: Central Surgical Association, Montreal, Canada. A. D. McLachlin, Victoria Hospital, London, Ontario, Canada.

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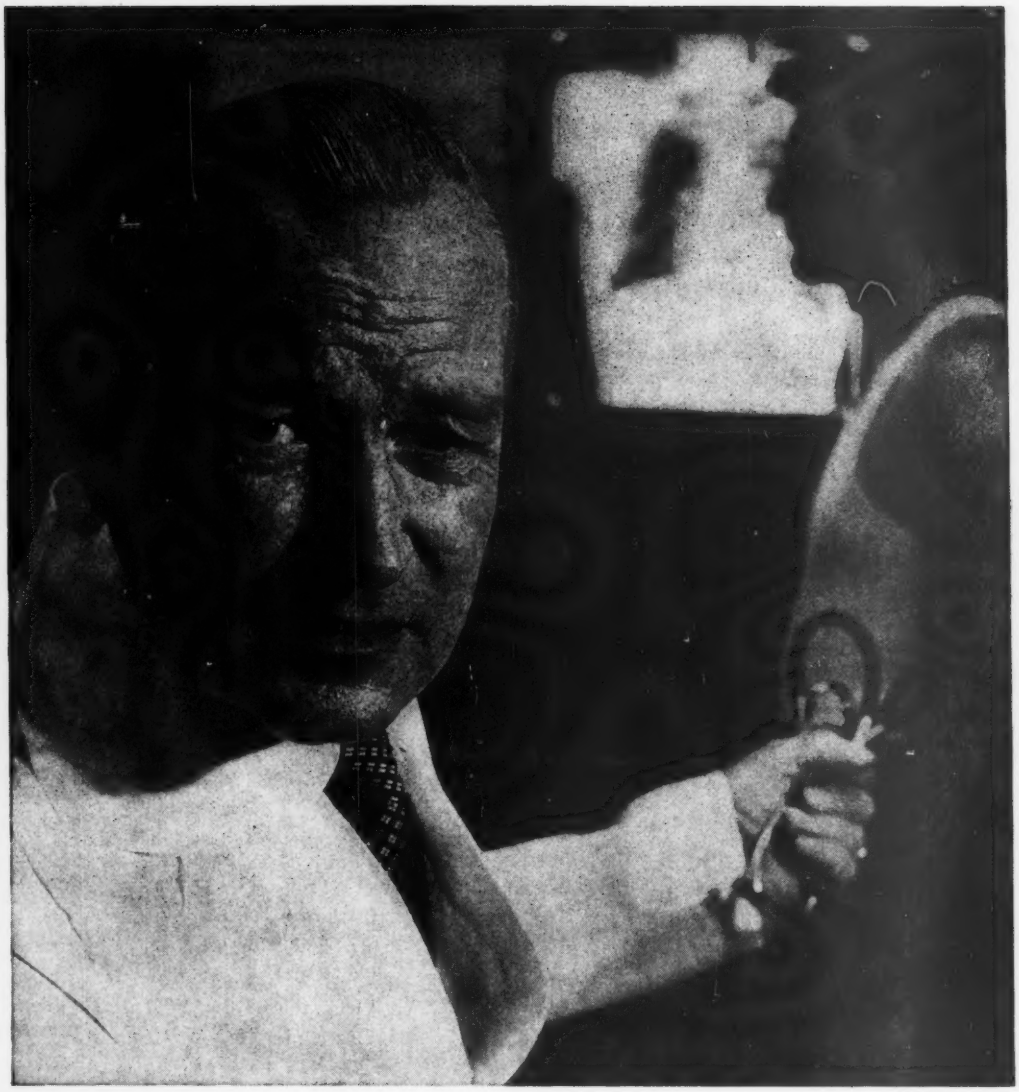

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